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Clinical Pharmacokinetics and Pharmacodynamics

Concepts and Applications

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Drug Interactions

OBJECTIVES

The reader will be able to:

- Define the following terms: additivity, antagonism, displacer, combination products, competitive inhibition, drug interaction, inhibition constant, isobologram, mechanism-based inhibition, noncompetitive inhibition, synergism, therapeutic drug interaction.
 - Discuss the graded nature of drug interactions, and provide two examples involving reversible inhibition, two involving mechanism-based inhibition, and one involving induction.
 - Explain mechanistically and kinetically the difference between reversible and mechanism-based inhibition.
 - Ascertain whether pharmacokinetics or pharmacodynamics of a drug, or both, is altered by another drug, given response and unbound plasma drug concentration–time data following chronic administration.
 - Anticipate the likely changes in plasma and unbound concentrations with time when the pharmacokinetics of a drug is altered by concurrent drug administration.
 - Explain why displacement of plasma protein binding is unlikely to produce a clinically significant drug interaction.
 - Explain why the degree of interaction tends to be greater when the affected drug is administered orally than when administered parenterally, for drugs that are normally subjected to a high oral first-pass metabolic loss.
 - Explain why the risk of a severe interaction resulting from inhibition is greater in poor than extensive metabolizers, when the fraction of drug metabolized polymorphically in extensive metabolizers is high, and the inhibitor inhibits elimination via the other pathway(s).
 - Anticipate the likely changes in plasma and unbound concentrations with time when the pharmacokinetics of a drug is altered by concurrent drug administration.
 - Show graphically the consequence of a pharmacokinetic drug interaction when the mechanism and the circumstances of its occurrence are given.
 - Explain why the combination of two agonists or two antagonists of the same receptor may not produce a greater response than that achieved with any one of them.
-

Patients commonly receive two or more drugs concurrently; indeed, inpatients on average receive five drugs during a hospitalization, and many, particularly elderly, patients may be taking concurrently eight or more drugs, as discussed in Chapter 14, *Age, Weight, and Gender*, Fig. 14-4. In addition, with an increasingly aged population, the issue of polypharmacy is of ever greater concern. The reasons for multiple-drug therapy are many. One reason, as discussed in Chapter 9, *Therapeutic Window*, is that drug combinations have been found to be beneficial in the treatment of some conditions, including various cardiovascular diseases, infections, and cancer. Another reason is that patients frequently suffer from several concurrent diseases or conditions, and each may require the use of one or more drugs, in which case the number of drug combinations is huge. Furthermore, drugs may be prescribed by clinicians in different medical specialties each of whom may be not fully aware of the therapeutic maneuvers of the others. Finally, patients may also self-medicate with over-the-counter medicines or herbal preparations. All of these reasons lead to a high probability of a **drug interaction** during drug therapy, especially in the elderly.

A drug interaction occurs when either the pharmacokinetics or pharmacodynamics of one drug is altered by another. In addition, constituents of some foods and herbal preparations may alter the pharmacokinetics or pharmacodynamics of drugs. Examples are inhibition by grapefruit juice of gut wall CYP3A and induction of this enzyme by St. John's wort, discussed in Chapter 7, *Absorption*, and Chapter 12, *Variability*. As the principles are the same as for drugs, such food and herbal drug interactions are not considered further, although they can be therapeutically important.

The potential for interactions among drugs within the body are almost limitless and are a source of variability in drug response. Many regard drug interactions as all-or-none, viewing them either as occurring or not, whereas in reality, most drug interactions, whether pharmacokinetic or pharmacodynamic in nature, are graded, depending on the concentration of the interacting drugs, and hence on the dosage regimens and pharmacokinetics of the drugs. Few of these interactions are of a type or of a sufficient magnitude to be clinically important. However, a number are and the risk of them occurring increases with the number of drugs that the patient is taking. A **therapeutic drug interaction** has then occurred. It is prudent to provide a cautionary note for those situations in which the two (or more) drugs need to be coprescribed. Some examples are listed in Table 17-1; in most cases, the interaction results in an exaggerated response of the affected drug, but not always so. Reduced activity can arise because the perpetrating drug either is an antagonist, reduces bioavailability, or increases clearance. Occasionally, the magnitude of the interaction is so great as to contraindicate the simultaneous use of the drugs. Very occasionally, the interaction has been so much more severe than anticipated and the likelihood of the combination being inadvertently given so great to cause either the affected or offending drug to be removed from the market. Examples are the antihistamines terfenadine and astemizole, the antihypertensive mebifredril, the statin cerivastatin, and cisapride, used to treat heartburn. However, the drugs were not removed from the market until some major clinical adverse events, sometimes fatal, occurred. Inadvertent, and potentially avoidable, adverse drug interactions also comprise a significant source of hospital admissions.

Not all patients receiving several interacting drugs elicit a therapeutically significant interaction. Often, it is just a few. The reasons for these differences in response among patients are manifold. Included are individual differences in the dosage regimen and duration of administration of each drug, in the sequence of drug administration, and in patient adherence. Pharmacodynamic and pharmacokinetic differences in genetics, concurrent disease states, and many other factors also contribute. Thus, the circumstances associated with a clinically significant interaction in an individual should always be carefully documented.

A pharmacodynamic interaction can arise for various reasons. These include the interacting drug complementing the action of the other, such as the use of a thiazide diuretic and a β -blocker, each acting by a different mechanism to lower blood pressure. Alternatively, the interacting drug may act as an antagonist or agonist at the same receptor site as the other drug, and, if an agonist, it may act additively or synergistically. The effect is

TABLE 17-1 Classification and Examples of Drug Interactions to Be Avoided**Pharmacodynamic Interactions**

Response		Example	Comment
	↑*	Diphenhydramine ↔ Alcohol [†]	Mutual sedative effects.
	↓	Naloxone → Fentanyl [‡]	Naloxone antagonizes the analgesic effect of the opioid fentanyl and can precipitate withdrawal symptoms.

Pharmacokinetic Interactions

Parameter			
Oral Bioavailability	↑	Saquinavir → Midazolam	Saquinavir inhibits intestinal CYP3A4-mediated metabolism of midazolam.
	↓	Antacids → Chloroquine	An interval of at least 4 hr is needed to avoid reduced absorption of chloroquine.
Volume of Distribution	↓	Quinidine → Digoxin	Quinidine reduces the tissue distribution of digoxin, causing need to reduce loading dose.
Metabolic Clearance	↑	Rifampin → Warfarin	Rifampin strongly induces hepatic microsomal enzymes.
	↓	Erythromycin → Sildenafil	Erythromycin strongly inhibits CYP3A4; major enzyme responsible for sildenafil metabolism.
Renal Clearance	↓	Diuretics → Lithium	By causing sodium loss, diuretics can reduce the renal clearance of lithium, and increase lithium retention, with potential toxicity.

*↑ Denotes increase, ↓ decrease in pharmacodynamic response or pharmacokinetic parameter value.

[†]↔ Denotes a mutual interaction, each affecting the other.

[‡]→ Denotes a unidirectional interaction; the arrow points to affected drug.

additive if the combined effect is that expected based on the concentration–response curves for each drug given independently. **Synergism** occurs when the effect produced with the two drugs is even greater than expected had the effect been additive.

In the case of pharmacodynamic interactions, for which the mechanism of action of each compound is known, the interaction is generally predictable and, if undesirable, is avoidable. The same is increasingly true of pharmacokinetic interactions, and when the interaction is desirable, the interacting drugs are often prescribed as combinations of fixed doses, although in such cases, there is commonly only one active principle; the second compound interacts to overcome an existing limitation in one or more aspects of the pharmacokinetics of the affected drug to increase its exposure–time profile at the target site for a given dose. Examples of pharmacokinetically driven beneficial combination products are listed in Table 17-2. Detailed aspects of some of these are discussed later in this chapter. Furthermore, most attention clinically in the area of drug interactions has been directed to changes in systemic exposure of drugs, and this forms the major emphasis of the current chapter.

Before considering drug interactions in greater detail, two final general comments need to be made. The first concerns the sequence of drug administration. A drug interaction is most likely to be detected in clinical practice when the interacting drug is initiated or withdrawn. For example, given the usual variability in patients' responses to

TABLE 17-2 Pharmacokinetically Driven Combination Products

Drug combination	Indication	Rationale for combination
Lopinavir/Ritonavir	AIDS	Ritonavir increases the systemic exposure, and decreases interpatient variability, of lopinavir by increasing its oral bioavailability and decreasing its clearance by inhibiting its CYP 3A4-catalyzed metabolism. It also allows for a reduced daily dose of lopinavir and a decrease in the frequency of dosing, every 12 hr versus 8 hr.
L-Dopa/Carbidopa	Parkinson's disease	Carbidopa increases the systemic exposure, and decreases interpatient variability, of L-dopa by inhibiting the decarboxylase enzyme responsible for L-dopa metabolism in intestinal, hepatic, and renal tissues. It allows for a reduced dosage of L-dopa and a more prolonged systemic exposure.
Imipenem/Cilastatin	Urinary tract infection	By inhibiting renal dehydropeptidase, responsible for metabolism of imipenem in the kidney, cilastatin increases the urinary tract concentrations of this antibiotic.
Amoxicillin/Cavulanate	Systemic infection	Some microorganisms are resistant to amoxicillin; they produce β -lactamases that destroy this antibiotic locally. Cavulanate overcomes this resistance by inhibiting β -lactamases, thereby increasing the local antibiotic exposure.

drugs, it is unlikely that a drug interaction would be detected if the affected drug is titrated to response in a patient already stabilized on the drug causing the interaction. Certainly, the dosage regimen of the affected drug would be different in *that* patient than would otherwise be the case, but the resulting regimen may still be within the normal range. In this case, only if the offending drug is withdrawn first, when the patient is stabilized on the drug combination, would the interaction be seen. The interaction would also have been detected if the interacting drug had been administered to the patient already stabilized on the original drug. However, sometimes the delay in full expression of the interaction may take so long that the clinician may not associate a change in patient response to the addition or withdrawal of the offending drug.

The second final comment concerns interactions involving drug transporters. Recall from Chapter 7, *Absorption*, that drugs that belong to class 1 of the Biopharmaceutics Classification System are highly soluble and permeable (e.g., Table 7-9); their absorption, and most of their disposition, is unaffected by transporters. The reason is that passive permeability tends to predominate. For analogous reasons drug interactions involving inhibition or induction of transporters, certainly in relation to intestinal absorption and probably hepatic processes, are not anticipated to affect the pharmacokinetics of such drugs. A clear potential exception exists at the blood-brain barrier, because there, owing to a low passive permeability, even for class 1 compounds, distribution may be permeability rate-limited. Inhibition of transporters there could result in altered brain permeability, and hence changes in both rate and extent of brain distribution, even of class 1 compounds. However, examples to date are rare. Class 1 drugs can nonetheless be inhibitors or inducers of transporters, and so potentially may affect the pharmacokinetics of drugs in classes 2 to 4 of the Biopharmaceutics Classification System.

CLASSIFICATION

One system of classifying drug interactions is to note whether drug response is increased or decreased. While perhaps clinically useful, this classification does not help to define the mechanism of the interaction. In this book, interactions are classified based on whether pharmacokinetics or pharmacodynamics is altered; occasionally, both are changed. Distinction between the two is made by relating response to the unbound plasma concentration of the pharmacologically active species. No change in the unbound concentration–response curve implies a pharmacokinetic drug interaction, which can arise either through a chemical interaction, such as inhibition of metabolism, or through a physiologic process, such as altered blood flow at an absorption site. The result is a change in one, or more, of the primary pharmacokinetic parameters, ka , F , V , CL_R , CL_H , that in turn alters the secondary pharmacokinetic parameters, such as half-life and f_e .

Before proceeding, a discussion of what is meant by the word *interaction* is worthwhile. Strictly speaking, this word implies a *mutual effect*. The interaction between two drugs, A and B, might thus be denoted by $A \leftrightarrow B$. An example is the competition between two drugs for a common binding site on albumin, one drug displaces but is also displaced by the other. Generally, however, the term **interaction** is interpreted more broadly to indicate any situation in which one drug affects another. For example, phenobarbital appears to reduce the absorption of the diuretic, furosemide, but the renal clearance of phenobarbital is increased by the diuresis produced by furosemide. This might be regarded as a **bidirectional interaction** and may be denoted by $A \rightleftharpoons B$. Clearly, in the case of mutual and bidirectional interactions, the measured response of one drug cannot be considered without also defining the level of the other.

When given in sufficient quantities, two drugs almost always affect each other; this may not be the case, however, at concentrations achieved in therapy. For example, the antibiotic enoxacin inhibits the metabolism of theophylline, but theophylline, at doses normally given, does not affect the response or the pharmacokinetics of enoxacin. This interaction is *unidirectional* and may be denoted by $A \rightarrow B$. In a unidirectional interaction, the unaffected Drug A (e.g., enoxacin) can be considered independently, but the change in response of the affected Drug B (e.g., theophylline) cannot be adequately defined without also considering the concentration–response curve of the effect of Drug A on Drug B. Examples of different types of drug interactions are listed in Table 17-1.

Finally, various terminologies have been used to describe the drugs involved in an interaction. The one producing the interaction has been called the offending drug, the precipitant, the perpetrator, or the villain (when the outcome is adverse). The one affected has been called the affected drug, the object, or the victim. In this chapter, these terms are used interchangeably.

Emphasis in this chapter is on pharmacokinetic drug interactions, although some aspects of pharmacodynamic interactions are considered toward the end. The physiologic concepts developed in Chapter 4, *Membranes and Distribution*, Chapter 5, *Elimination*, and Chapter 7, *Absorption*, together with the kinetic principles developed in Chapter 9, *Therapeutic Window*, Chapter 10, *Constant-Rate Input*, and Chapter 11, *Multiple-Dose Regimens*, form the basis for discussing many aspects of pharmacokinetic drug interactions. For convenience, in this chapter, the effect of one drug on another is examined under the separate headings of altered absorption, altered distribution, and altered clearance. However, it should be borne in mind that several pharmacokinetic parameters can be, and sometimes are, altered simultaneously, examples of which are subsequently discussed.

ALTERED ABSORPTION

It was stated in Chapter 6, *Kinetics Following an Extravascular Dose*, and Chapter 11, *Multiple-Dose Regimens*, that the more rapid the absorption process, the higher and earlier is the peak plasma concentration and that neither total area under the curve (AUC) after a single

dose nor AUC within a dosing interval at plateau after chronic dosing changes unless the bioavailability of the drug is altered. Therapeutic consequences of a change in either rate or extent of drug absorption were discussed in Chapter 11, *Multiple-Dose Regimens*.

Considered now are situations in which bioavailability is altered, with emphasis on changes in average plasma concentration with time during chronic dosing; an altered speed of absorption (k_a) changes only the degree of fluctuation around the average value. The events with respect to a constant rate of drug input are illustrated in Fig. 17-1.

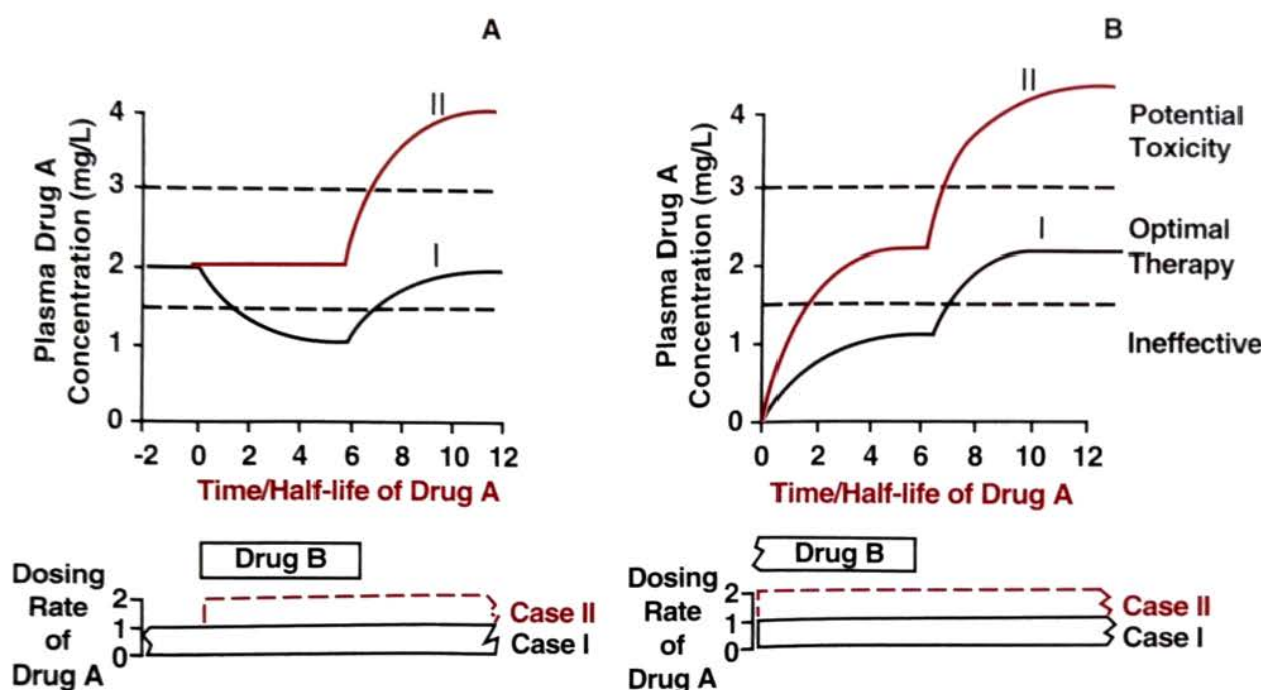


FIGURE 17-1. Altered absorption. As long as Drug B is administered, the bioavailability of Drug A is reduced by one half. For simplicity, Drug A is assumed to be given at a constant rate. The therapeutic concentration range of Drug A lies between 1.5 and 3 mg/L. **A.** Patient stabilized on Drug A. The plasma concentration of Drug A falls by one half (*Case I*), unless the dosing rate is doubled (*Case II*, color), when Drug B is concurrently administered. A problem potentially arises if administration of Drug A is not reduced to its preexisting rate when Drug B is removed (*Case II*, color). **B.** Patient stabilized on Drug B. An adequate concentration of Drug A is not achieved (*Case I*), unless the usual dosing rate of this drug is doubled (*Case II*, color). When Drug B is withdrawn, there is a potential problem similar to that considered in A. In both **A** and **B**, the time course of events for Drug A is determined by its half-life.

Figure 17-1A depicts the situation in which a patient stabilized on Drug A, now receives Drug B, which reduces the bioavailability of Drug A. It is apparent that if no steps are taken to change the dosing rate of Drug A, its concentration falls to a lower plateau, *the time being determined by the elimination half-life of this drug*. Suppose that it is then noticed that the patient is no longer being treated effectively with Drug A, and that, having recognized the problem, the offending drug is withdrawn. The concentration of Drug A would then return to the previous plateau value in 3.3 elimination half-lives. Therapeutic control would again be restored. Alternatively, on another occasion, in anticipation of the problem but desiring to give the two drugs together, the dosing rate of Drug A is increased appropriately at the time that Drug B is introduced. As long as Drug B continues to be administered, therapeutic control is satisfactory. A problem arises, however, if Drug B is subsequently withdrawn, but the dosing rate of Drug A is not correspondingly reduced. Then, in 3.3 elimination half-lives, the concentration of Drug A reaches a higher plateau where toxicity is likely.

Another possible situation is one in which Drug A is added to the regimen of a patient stabilized on Drug B (Fig. 17-1B). Here, as before, optimal therapy with Drug A in the presence of Drug B is achieved only if the usual dosing rate of Drug A is appro-

proportionately increased. However, the danger of the concentration of Drug A rising too high, if the dosing rate of Drug A is not readjusted when Drug B is withdrawn, must always be kept in mind.

The situations just considered emphasize the dependence of time course of events on the half-life of the affected drug. Thus, for affected drugs with very long half-lives, such as phenobarbital (4-day half-life), changes in response are insidious, occurring over several weeks, and the clinician may not associate the interaction with the causative drug, which was either initiated or stopped quite some time previously.

ALTERED DISTRIBUTION

One drug can affect the kinetics of tissue distribution of another, for example, by changing tissue perfusion, a hemodynamic interaction. This occurs during general anesthesia when perfusion to many tissues is reduced. However, primary consideration here is directed to changes in the extent of distribution, reflected in changes in volume of distribution, V . Recall the relationship for drugs of $V \geq 50 \text{ L}$ ($\geq 0.7 \text{ L/kg}$)

$$V = V_P + V_T \frac{f_u}{f_{uT}} \quad 17-1$$

from which it is seen that V can be altered by changes in either f_u or f_{uT} , the fraction unbound in that tissue space. Although theoretically possible, changes in V_P , the volume of plasma, and V_T , the volume of aqueous space of tissues into which drug distributes, are extremely unlikely to occur. Recall also when $V < 50 \text{ L}$, and particularly for very low volume of distribution drugs ($V < 15 \text{ L}$ or $< 0.20 \text{ L/kg}$), we need to take into account that changes in f_u give rise to corresponding changes in binding to the same plasma protein residing in the interstitial spaces. Another cause of an altered distribution, considered later, is one in which a drug inhibits the uptake or efflux by a transporter of another drug whose distribution is permeability rate-limited.

The most common explanation for altered distribution in a drug interaction is displacement. Displacement is the reduction in the binding of a drug to a macromolecule, usually a protein, caused by competition of another drug, the **displacer**, for common binding site(s). The result is a rise in f_u or f_{uT} , or in both. Sometimes, binding is diminished through an allosteric effect. The second drug, binding at another site, induces a conformational change in the protein, thereby reducing the affinity of the first drug for the protein. Occasionally, an allosteric effect causes an enhanced affinity between drug and protein; drug binding is then increased.

CONDITIONS FAVORING DISPLACEMENT

Two conditions must be met before substantial displacement occurs. First, in the absence of a displacer, the drug must be bound mostly to a protein, that is, its f_u or f_{uT} must be low. Obviously, if a drug is not bound, it cannot be displaced. Second, the displacer must occupy most of the binding sites, thereby substantially lowering the number of sites available to bind drug.

Table 17-3 lists two groups of acidic drugs that bind to albumin. As can be seen, not all drugs bind to, and hence compete for, the same primary binding site on albumin. Albumin and some other proteins have several binding sites, each exhibiting some degree of specificity. Hence possessing an acidic function is not in itself a sufficient criterion for predicting the ability of one acidic drug to displace another. Moreover, even though almost all those drugs that compete for the same site have a high affinity for albumin, only a few are generally listed clinically as displacers, such as salicylic acid, valproic acid, and ibuprofen. This list is limited because the bound plasma concentration achieved during therapy must approach or exceed 0.6 mM (140 g/3 L), the molar concentration of plasma albumin. For a substance with a molecular weight of 250, this concentration corresponds

TABLE 17-3 Binding of Selected Drugs to Albumin**Drugs That Bind to and Compete for One of Two Sites, Designation I and II, on Albumin**

Site 1*	Site 2†
Chlorothiazide	Benzodiazepines
Furosemide	Cloxacillin
Indomethacin†	Dicloxacillin
Naproxen†	Glibenclamide
Phenytoin	Ibuprofen
Sulfadimethoxine	Indomethacin†
Salicylic acid	Naproxen†
Tolbutamide†	Oxacillin
Valproic acid	Probenecid
Warfarin	Tolbutamide†

*Archetype: warfarin.

†Archetype: diazepam.

‡These drugs bind to both sites.

to 150 mg/L, but even a concentration 20% of this value, 30 mg/L, may increase f_u significantly. These concentrations are approached during salicylate and valproic acid therapy and during high-dose ibuprofen therapy, because these drugs are given in doses approaching 1 g, they are of low molecular weight (138, 144, and 204 g/mol, respectively) and they possess relatively small volumes of distribution, 10 to 15 L/70 kg. High molar concentrations could also be achieved with lower daily doses if the compound has a long half-life relative to dosing interval, thereby resulting in extensive accumulation. For example, approximately 40% of a 25-mg daily dose of leuflonamide is converted to a very highly albumin-bound active metabolite (molecular weight = 270 g/mol), which, because of its very low clearance (0.01 L/hr) and long half-life (~10 days), yields plateau plasma metabolite concentrations in the order of 50 mg/L.

Displacers share an expected common property (i.e., their f_u values change with plasma concentration). With most sites occupied by the displacer, the fraction unoccupied is sensitive to a change in the concentration of displacer. Therefore, displacers must show concentration-dependent disposition kinetics (Chapter 16, *Nonlinearities*).

So far, distinction has been made between displacer and displaced drug, but it should be apparent that this classification is arbitrary. Valproic acid is said to displace warfarin from albumin, but only because the therapeutic plasma concentration of valproic acid (70 mg/L; 0.48 mM) approaches the molar concentration of albumin (0.6 mM), whereas that of warfarin (1–4 mg/L; 0.003–0.01 mM) does not. Both drugs have high affinity for the same site on albumin, and if the concentrations were reversed, warfarin would be called the displacer.

The conclusions drawn from the interactions between acidic drugs and albumin are generally applicable to all drug–protein interactions, bearing in mind the widely differing molar concentrations of the various binding proteins in plasma (Chapter 4, *Membranes and Distribution*). For example, the molar concentration of α_1 -acid glycoprotein, which avidly binds many basic drugs, is low (0.009–0.023 mM), and therefore displacement interactions can occur at plasma concentrations much lower than those required for displacement of acidic drugs from albumin (600-mM concentration). Substantial displacement of bases from tissue binding, observed as a decrease in V , is less likely, however, because unlike in

plasma, where α_1 -acid glycoprotein is the primary binding protein, there are relatively high concentrations of the major binding proteins, the acidic phospholipids, in tissues. Or, stated differently, the unbound tissue concentrations of many bases are well below the K_d of the binding constituents.

THERAPEUTIC IMPLICATIONS

Displacement interactions in plasma have been studied primarily *in vitro*. The potential displacer is added at therapeutic concentrations to a sample of plasma containing the drug, and changes in its binding are measured. Substantial displacement is frequently demonstrated, yet this may be of little therapeutic consequence. Much depends on whether the events are acute or occur at plateau during chronic therapy.

Acute Events. Two situations can be envisaged. One involves the administration of a loading dose of drug to a patient already stabilized on a displacer. The other involves the administration of a dose of displacer to a patient already stabilized on a drug. In both situations, the question of altering the usual dose of drug arises only if the unbound drug concentration increases above the therapeutic range, in the presence of the displacer. The extreme situation is one in which the displacer is administered as an intravenous (i.v.) bolus, which initially is restricted essentially to plasma, causing a transient rise in the unbound displaced drug there, before falling back as both displacer and unbound displaced drug moves down their respective concentration gradients into tissues. Accordingly, if response tracks unbound plasma concentration more rapidly than the kinetics of redistribution, a transient increase in response might be anticipated. In practice, this last situation is unlikely to arise, because to minimize the risk of adverse reactions, most intravenously administered drugs are given as a short-term infusion rather than as a bolus.

Less transient events are expected if, after redistribution, the unbound volume of distribution (V_u) of displaced drug decreased significantly, because this will produce a sustained increase in unbound drug for a given amount in the body. Such a decrease in V_u occurs only if, in the absence of the displacer, the drug is substantially bound in the body and the displacer causes significant displacement of drug from the major binding sites. For example, the unbound concentration rises if displacement occurs from sites on a plasma protein for a drug with a small volume of distribution, around 10 L/70 kg, or if displacement occurs from tissue-binding sites for a drug with a large volume of distribution. An example of the former situation is the displacement of warfarin from albumin-binding sites by naproxen. Displacement from tissue-binding sites would be expected to occur with high doses of bosentan and imirestat coadministered with drugs that bind to the same sites, given that these sites are saturated at such high doses (Chapter 16, *Nonlinearities*). However, these situations are relatively uncommon. More common is displacement from plasma-binding sites of a drug with a large volume of distribution. Then, because so little drug resides in plasma, relative to that in the body as a whole, only a minimal change in the unbound drug concentration, and hence response, occurs even when all the drug on the proteins are displaced, as discussed in Chapter 4, *Membranes and Distribution*. For example, if the volume of distribution is 100 L and 99% of the drug in plasma is bound ($f_u = 0.01$), then only 3% ($100 \times [1 - f_u] \cdot ([\text{plasma volume}]/V)$) of that in the body resides bound in plasma. Even if completely displaced, the small amount affected would redistribute throughout the rest of the body and so would only marginally increase the unbound body pool.

Returning to the example of warfarin, because the clinical response (prothrombin time) is so delayed and insensitive to acute changes in warfarin concentration (Fig. 8-7, Chapter 8, *Response Following a Single Dose*), no adjustment in dosage of this oral anticoagulant would be contemplated in the event of acute displacement, even though V_u is reduced. A more important consideration for most other drugs is the effect of

displacement on events at plateau, because most drugs, including displacers, are given chronically.

Events at Plateau. The influence of displacement on the unbound concentration at steady state (Cu_{ss}) depends on extraction ratio and route of administration of the affected drug.

Consider a drug with a *low extraction ratio*. Recall that clearance depends on f_u , but unbound clearance (CL_u) does not. Also recall the equalities (Eq. 5-2, Chapter 5, *Elimination*)

$$CL_u \cdot Cu = CL \cdot C \quad 17-2$$

and that for this class of drug, CL_u approximates CL_{int} . When drug is infused at a constant rate, R_{inf} and steady state is achieved,

$$R_{inf} = CL_{int} \cdot Cu_{ss} = CL \cdot C_{ss} \quad 17-3$$

However, because intrinsic clearance is unaffected by displacement, the same is true of the value of Cu_{ss} . Thus, although displacement by increasing f_u increases clearance (and hence causes the total plasma concentration to fall), no change in response and therefore in dosing rate is anticipated at steady state. Neither is any change anticipated in $Cu_{av,ss}$ upon chronic multiple dosing.

Now consider a drug with a *high extraction ratio*. Because blood clearance is unaffected by displacement, the steady-state blood concentration is also unaffected following a constant-rate i.v. infusion. However, as binding is diminished, ($f_u \uparrow$), Cu_{ss} and therefore response to the drug must be increased as $Cu_{ss} = f_u \cdot C_{b,ss}$. The maintenance dosing rate of the drug may need to be reduced. Although an extremely uncommon situation, conceivably the opioid fentanyl, which has a high extraction ratio, is reasonably highly bound ($f_u = 0.15\text{--}0.2$) and administered both intravenously and transdermally, fulfills the condition, but no clinically significant displacement interaction has been reported.

Prediction of the outcome when a drug with a high extraction ratio is given orally and when elimination occurs predominantly in the liver is difficult. In the presence of the displacer, both unbound drug clearance and oral bioavailability decrease (see Chapter 7, *Absorption*); the effect of displacement on the unbound drug concentration at plateau is therefore likely to be relatively small. Irrespective of any effect of displacement, however, the unbound concentration at plateau is lower than that achieved following an equivalent i.v. infusion.

The events predicted at plateau before and after displacement for drugs of low and high extraction are shown in Fig. 17-2. Shown in Fig. 17-3 are the total and unbound plateau plasma concentrations of the antiepileptic drug phenytoin in patients before and after receiving valproic acid, another antiepileptic drug, which displaces phenytoin from albumin binding sites. As predicted for a drug of low extraction, the unbound concentration is unaltered, whereas the total plasma concentration is decreased. Accordingly, based on these observations, there is no need to alter the dosing rate of phenytoin in patients receiving valproic acid.

Kinetic Features. Both acute events and events at plateau have been discussed. Remaining to be discussed are the kinetic consequences of displacement on approach to plateau under the usual condition in which both drug and displacer are given chronically. To do so, first consider the expected changes in disposition kinetics of a drug upon displacement.

Disposition Kinetics. The subsequent points summarize those made in Chapter 5, *Elimination*. Because clearance of a drug with a high extraction ratio is unaffected by displacement, the half-life changes with volume of distribution. In contrast, for a drug of low extraction, because unbound clearance, CL_u (CL_{int}) does not change, half-life either remains constant (when V_u does not change) or shortens (if V_u decreases) with displacement from plasma proteins.

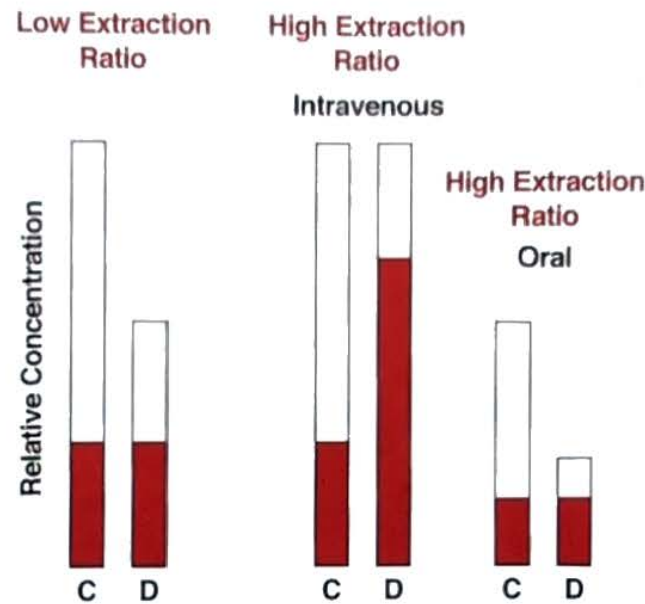


FIGURE 17-2. Changes, at plateau, in the total (□ and ■) and unbound (■) concentrations (D = displaced; C = control) depend on the extraction ratio of the drug and route of drug administration. For a drug of low extraction ratio, diminished binding ($f_u \uparrow$) reduces the total, but not the unbound, concentration regardless of the route of administration. For a drug of high hepatic extraction ratio, clearance, and so total concentration, is unaffected by diminished binding when the drug is given intravenously. The unbound concentration, however, is elevated. Because diminished binding decreases oral bioavailability of the highly cleared drug, the likely outcome of displacement after oral administration is a decrease in the total concentration and little or no change in the unbound concentration. The actual change depends on whether the effect on oral bioavailability or clearance predominates.

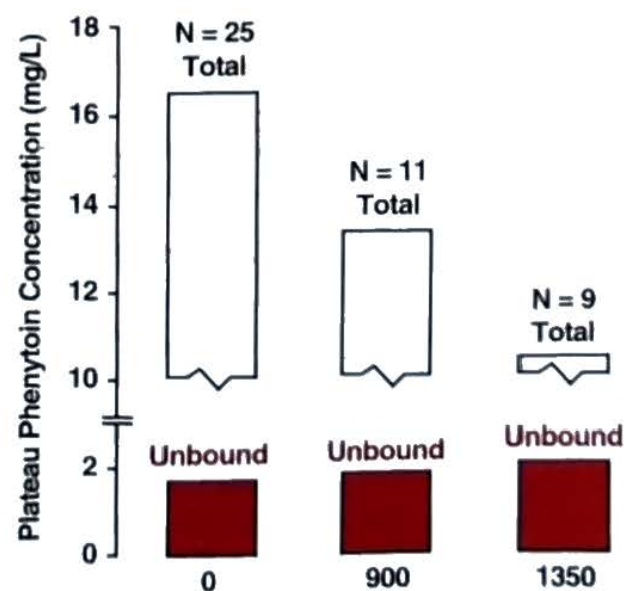


FIGURE 17-3. The valproic acid–phenytoin interaction involves displacement only. Although plasma protein binding of phenytoin is decreased when sodium valproate is administered chronically to a group of patients stabilized on phenytoin, with a resultant fall in the steady-state plasma phenytoin concentration, there was no substantial change in the unbound phenytoin concentration (colored). These observations are consistent with a displacement interaction of phenytoin by valproic acid. Note that the degree of phenytoin displacement depends on the dose of sodium valproate. Of the 25 patients stabilized on phenytoin, 11 received 900-mg sodium valproate per day; 9 received a 1350-mg daily dose; and some received both regimens. (From: Mattson RH, Cramer JA, Williamson PD, Novelly, RA. Valproic acid in epilepsy: clinical and pharmacological effects. *Ann Neurol* 1978;3:20–25.)

Plasma Concentration–Time Profile. Although there are many possible combinations of events, only one common situation is considered. In this case (Fig. 17-4), the displacer, which has a longer half-life than that of the drug, is added to the regimen of a patient stabilized on a low extraction ratio drug. To simplify matters, both drug and displacer are administered by constant-rate infusion and both are assumed to always be at distribution equilibrium. Although these conditions are somewhat restrictive, the situation chosen does illustrate the importance of both kinetics and the manner of drug administration on the likely therapeutic outcome on approach to plateau.

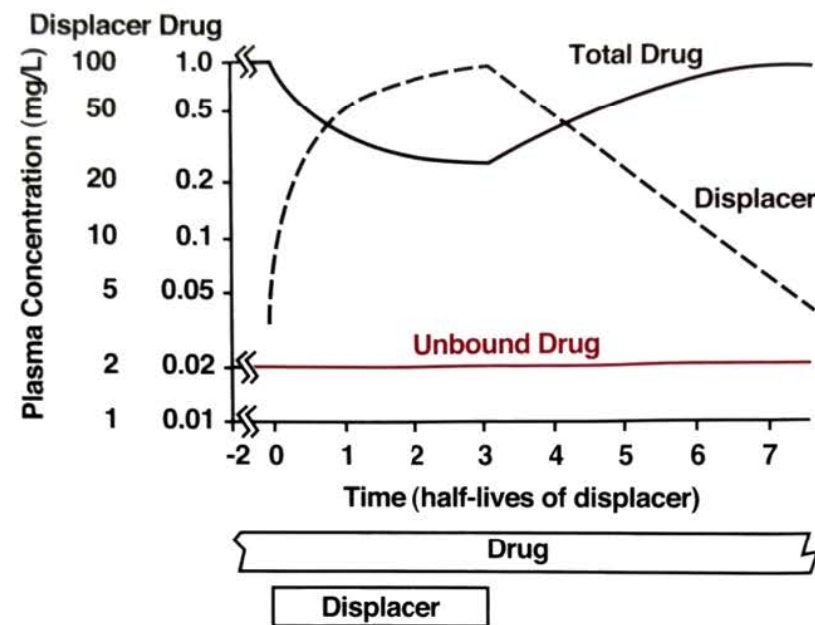


FIGURE 17-4. When constantly infused, the unbound concentration (*color*) of a drug with a low extraction ratio remains virtually unchanged if a displacer with a long half-life, relative to the drug, is either infused or withdrawn. The change in total plasma drug concentration reflects the displacement.

Notice in Fig. 17-4 that slow accumulation and correspondingly slow elimination of the displacer results in insignificant changes in the unbound drug concentration and therefore response. This is a consequence of the kinetics of the displacer being slower than that of the drug. The concentration of the displacer is changing so slowly relative to that of the drug that at all times the drug is at a virtual steady state, with rate of elimination ($CL_{int} \cdot Cu_{ss}$) matching the rate of input. That is, although there is a tendency for the unbound drug concentration to rise above the concentration at steady state during accumulation of the displacer, there is an opposing tendency for the unbound concentration to fall because the rate of elimination ($CL_{int} \cdot Cu$) would then exceed the rate of administration ($CL_{int} \cdot Cu_{ss}$). The reverse tendencies occur on stopping the displacer, but once again, they balance each other out. Accordingly, although the unbound concentration remains essentially unaltered, the total plasma drug concentration changes inversely with that of the displacer, reflecting the changing degree of displacement. A transient change in unbound concentration might occur if the kinetics of the drug, rather than that of the displacer, had been the slower.

In the case just discussed, no change in effect, and hence in the dosage regimen of the drug, is anticipated even though displacement has occurred. If only response were monitored, displacement would not have been suspected.

ALTERED CLEARANCE

A reduction in unbound clearance is potentially the most dangerous type of drug interaction. The unbound drug concentration can then rise to a toxic level, unless a reduction

in dosage is made. Consequently, it is extremely important to be able to identify, characterize, and, where possible, avoid this type of adverse interaction. Interactions involving an increase in unbound clearance, because of induction, also occur causing the unbound drug concentration to fall, potentially resulting in a diminished response. Although generally of less concern, a diminished response can sometimes lead to failure of therapy with its attendant risks. Both inhibition and induction often have a high degree of specificity involving a specific enzyme. Examples of inhibitors and inducers of the major drug-related CYP enzymes are illustrated in Fig. 17-5. Inhibition and induction of transporters also occurs, but currently far less is known about specific transporters than enzymes.

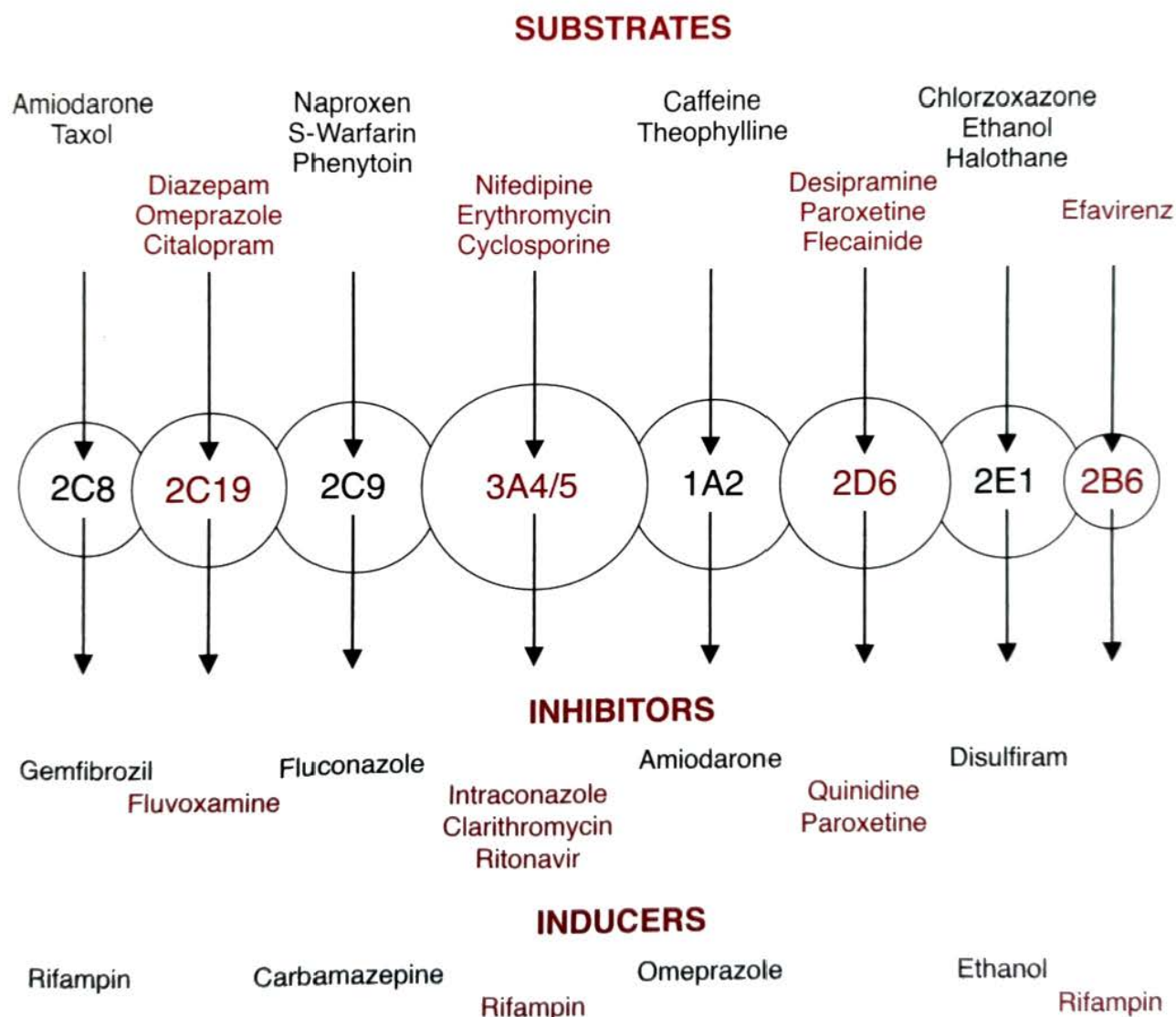


FIGURE 17-5. Graphic representation of the different forms of cytochrome-P450 (*circles*) in humans with different but some overlapping substrate specificities. The arrows indicate single metabolic pathways. Representative substrates are listed above for each enzyme. Also listed are relatively selective inhibitors and inducers of the enzymes.

INHIBITION

Inhibition of drug metabolism is the major cause of reduced unbound clearance. A reduction can also occur on inhibition of biliary and renal secretion and on inhibition of an uptake transporter, when uptake permeability rate-limits, or becomes the rate-limiting step in, organ clearance. Inhibition is of two general types, **competitive** and **non-competitive**. Competitive inhibition occurs when inhibition can be overcome by raising sufficiently high the concentration of the substrate. It is the most common type of

inhibition. The net effect is an increase in the apparent K_m of the substrate but no change in its V_m . The term is normally applied to enzyme metabolism, but, more broadly, can be applied also to transport processes, with an associated increase in observed K_T but no change in T_m . Noncompetitive inhibition, which although less common is no less important, involves independent inhibition of an enzyme and, unlike competitive inhibition, cannot be overcome by raising the concentration of the substrate; it is characterized by a decrease in V_m but no change in K_m of the substrate. One common type of noncompetitive inhibition is **mechanism-based inhibition** involving the formation of a reactive metabolite that effectively covalently binds to, and permanently inactivates, the enzyme. We first focus on competitive inhibition and then mechanism-based inhibition.

Competitive Inhibition

A Case Study. Some patients receiving theophylline develop nausea when enoxacin, an anti-infective quinoline, is added to the theophylline regimen. The nausea is associated with an elevated concentration of theophylline caused by enoxacin inhibiting the metabolism of theophylline.

The dramatic rise in the trough plasma concentration of theophylline when enoxacin is added to the regimen, and the return to the pre-enoxacin value when enoxacin is withdrawn, are illustrated in Fig. 17-6. Notice that it takes approximately 4 days of enoxacin

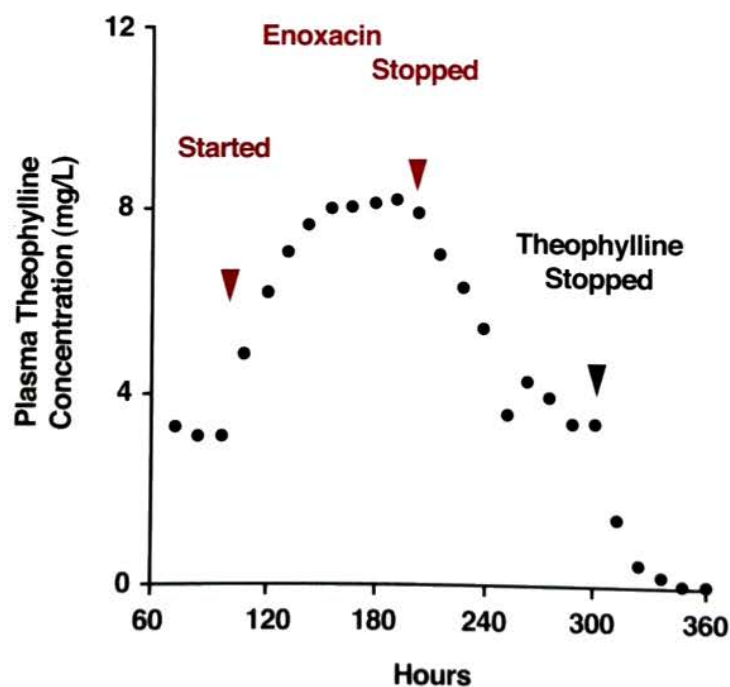


FIGURE 17-6. Enoxacin inhibits theophylline elimination. Subjects received 150-mg theophylline (in a controlled-release dosage form) orally every 12 hr for 12 days (288 hr). By 72 hr, as expected, the trough has reached a plateau with an average concentration within a dosing interval of 4.8 mg/L (*not shown*). Enoxacin was given, 400 mg orally every 12 hr for 4 days, starting 96 hr into the theophylline regimen. On addition of enoxacin, the mean trough theophylline concentration rose to a new and higher plateau (average interdose concentration of 9 mg/L, *not shown*). The time course of the rise was determined by the half-life of theophylline in the presence of enoxacin (22 hr). Although, on withdrawal of enoxacin, the plasma theophylline concentration fell toward the pre-enoxacin value (average interdose concentration of 4 mg/L, *not shown*), the concentration of enoxacin must have been sufficient to maintain appreciable inhibition for some time. Otherwise, the return of theophylline to the pre-enoxacin concentration would have been much quicker, being determined by the normal half-life of theophylline, 8.8 hr. (From: Rogge MC, Solomon WR, Sedman AJ, et al. The theophylline-enoxacin interaction: II. Changes in the disposition of theophylline and its metabolites during intermittent administration of enoxacin. *Clin Pharmacol Ther* 1989;46:420–428.)

administration for theophylline concentration to rise to the new plateau and a similar time for it to return to the pre-enoxacin value after enoxacin is withdrawn.

A more quantitative picture of the events may be gained from two equations. One, previously examined (Eq. 11-8, Chapter 11, *Multiple-Dose Regimens*), defines the average concentration of drug at plateau

$$C_{ss,av} = \frac{F \cdot Dose}{CL \cdot \tau} \quad 17-4$$

The other equation defines the new (and longer) half-life of theophylline ($t_{1/2, inhibited}$) in relation to the normal half-life ($t_{1/2, normal}$).

$$t_{1/2, inhibited} = t_{1/2, normal} \cdot \frac{CL_{normal}}{CL_{inhibited}} \quad 17-5$$

where CL_{normal} and $CL_{inhibited}$ are the clearances of theophylline in the absence and presence of the inhibitor, respectively. Equation 17-5 follows from the equation $k = CL/V$ and from the knowledge that enoxacin does not affect the volume of distribution of theophylline, a drug only weakly bound in plasma and tissue.

The half-life of theophylline in the absence of enoxacin is 8.8 hr, estimated from the declining concentration when theophylline administration is stopped (day 13). As expected, with such a short half-life, the plateau concentration ($C_{av,ss}$), approximately 4 mg/L, is reached within 2 days of starting the theophylline regimen.

Enoxacin is rapidly absorbed and immediately inhibits theophylline metabolism when administered on the fifth day into the theophylline regimen. With continual administration of the same dosage regimen of theophylline, its plasma concentration rises to a new plateau, approximately 9 mg/L, determined by the new, and lower, clearance value ($CL_{inhibited}$). Accordingly, by reference to Eq. 17-4,

$$\frac{CL_{inhibited}}{CL_{normal}} = \frac{C_{ss,av,normal}}{C_{ss,av,inhibited}} \quad 17-6$$

and on substituting 4 mg/L and 9 mg/L for $C_{av,ss,normal}$ and $C_{av,ss,inhibited}$, one obtains $CL_{inhibited} = 0.44 \times CL_{normal}$. That is, enoxacin reduces the clearance of theophylline by 56%. This calculation is based on the assumption that the bioavailability of theophylline, which is usually well absorbed, is unaffected by enoxacin.

The new half-life of theophylline in the presence of the inhibitor can now be calculated by appropriately substituting into Eq. 17-5; it is 22 hr ($8.8 \text{ L} \times 1/0.44$). This longer half-life explains why it takes 4 days, rather than the usual 2 days, to reach the new plateau. It is also consistent with the observation that the plasma concentration of theophylline (6.5 mg/L) midway between the previous and new plateaus occurs 1 day after administering enoxacin.

The slow return of the plasma theophylline concentration to the pre-enoxacin value on withdrawal of enoxacin remains to be explained. Although withdrawn, the concentration of enoxacin in plasma ($t_{1/2} = 4\text{--}5$ hr) persists at a sufficiently high value to continue to inhibit the metabolism of theophylline for a considerable period of time. As such, the half-life of theophylline, which controls the return of theophylline to its pre-enoxacin concentration, remains elevated for some time. Had inhibition ceased immediately upon withdrawing enoxacin, the half-life of theophylline would have reverted to its control value, 8.8 hr, and the return of theophylline concentration to the pre-enoxacin value would have been much quicker.

A Graded Effect. The last statement needs some amplification. The inhibition of theophylline by enoxacin is not an all-or-none effect, but rather, as with all interactions, a graded one. The degree of inhibition varies with the plasma concentration, and hence dose, of enoxacin, as illustrated in Fig. 17-7. Shown are both the plasma

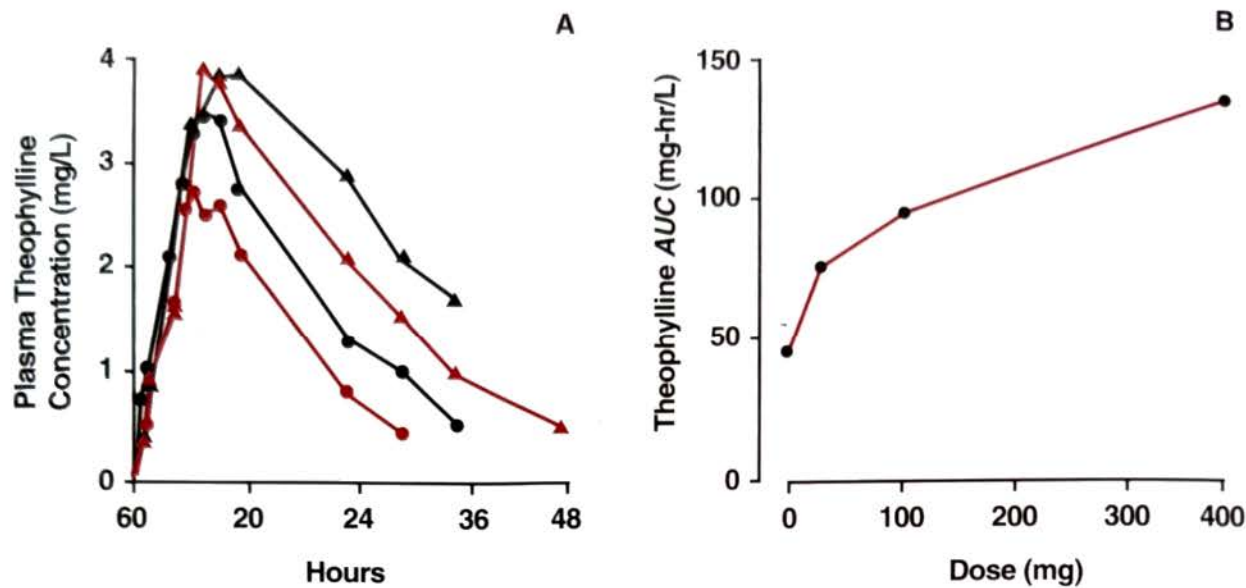


FIGURE 17-7. The inhibition of theophylline elimination by enoxacin is graded, as evidenced by the prolongation in half-life of decline of plasma theophylline concentration (**A**) and increase in *AUC* (**B**) when a 200-mg dose of theophylline is administered alone (●) and during 7-day regimens of 25-mg (●), 100-mg (▲), and 400-mg (▲) enoxacin given every 12 hr. Data are the means of four subjects. (From: Rogge MC, Solomon WR, Sedman AJ, et al. The theophylline-enoxacin interaction: I. Effect of enoxacin dose size on theophylline disposition. *Clin Pharmacol Ther* 1988;44:579–587.)

concentration–time profiles and *AUC* of theophylline following a single dose of theophylline taken alone and at steady state during regimens of 25, 100, and 400 mg of enoxacin given every 12 hr. As expected for a drug of low clearance, both *AUC* and half-life of theophylline increase with inhibition. Notice that inhibition is evident even with the 25-mg enoxacin regimen and then increases, tending to approach an upper limit with the 400-mg regimen. Restated, even though the plasma enoxacin concentration falls after a 400-mg dose, inhibition persists, to varying degrees, for some time thereafter. Clearly, the longer the half-life of an inhibitor, the more persistent is inhibition on withdrawing it.

To appreciate more fully the graded nature of inhibition of metabolism, consider the following. Recall (Chapter 16, *Nonlinearities*) that for each metabolic pathway operating according to Michaelis-Menten-type kinetics

$$\text{Rate of metabolite formation} = \frac{V_m}{K_m} \cdot C_{u_{cell}} \quad 17-7$$

when the unbound drug concentration at the (intracellular) enzyme site, $C_{u_{cell}}$ is well below the Michaelis-Menten constant, K_m . Or, expressed in terms of intrinsic clearance associated with metabolite formation, $CL_{int,f}$.

$$CL_{int,f} \cdot C_{u_{cell}} = fm \cdot CL_{int} \cdot C_{u_{cell}} \quad 17-8$$

where fm is the fraction of the drug that is converted to the metabolite. Inhibition decreases $CL_{int,f}$ of a metabolite. A common model to describe metabolism in the presence of the inhibitor is

$$\text{Rate of metabolism} = \frac{CL_{int,f} \cdot C_{u_{cell}}}{1 + C_{u_I}/K_I} = \frac{fm \cdot CL_{int} \cdot C_{u_{cell}}}{1 + C_{u_I}/K_I} \quad 17-9$$

where C_{u_I} is the unbound concentration of the inhibitor and K_I is the **inhibition constant**, given by the unbound inhibitor concentration that decreases $CL_{int,f}$ of the affected pathway by twofold. Clearly, the lower the K_I , the more potent is the inhibitor.

Two main conclusions may be drawn from Eq. 17-9. First, the degree of inhibition of a particular pathway depends on the unbound inhibitor concentration relative to its K_i . Many a compound has been shown to inhibit drug metabolism in vitro but fails to do so in vivo, because the unbound concentrations associated with therapeutic regimens of the inhibitor are well below its K_i value. Also, given that the concentration of the inhibitor generally varies with time after its administration, so does the degree of inhibition. Clinically, it is useful to classify an inhibitor as strong, moderate, or weak (Table 17-4), because this helps to decide whether the combination with a susceptible drug is either contraindicated or requires a reduction or no change in dosage. Clearly, this classification depends as much on the therapeutic concentration range of the inhibitor as on its K_i . If another clinical indication for the inhibitor requires a much lower or higher concentration, then its classification as an inhibitor when used for this indication may be different.

Second, the impact of inhibition on drug elimination depends on f_m and whether response lies with drug or metabolite formed. Inhibition has the most profound effect when the affected pathway is either obligatory for the elimination of the drug, that is

TABLE 17-4 Classification of Inhibitors by the Magnitude of Their Effect at Therapeutic Doses*

Strong ($\geq$ fivefold increase in AUC)	Moderate ($\geq$ two- but $<$ fivefold increase in AUC)	Weak ($\geq$ 1.25- but $<$ twofold increase in AUC)
CYP3A		
Clarithromycin [†]	Amprenavir	Cimetidine
Itraconazole	Aprepitant	
Ketoconazole	Diltiazem [†]	
Ritonavir [†]	Erythromycin [†]	
Telithromycin [†]	Fluconazole	
	Grapefruit juice [†]	
	Verapamil	
CYP1A2		
Fluvoxamine	Ciprofloxacin	Norfloxacin
	Propafenone	Verapamil
CYP2C9		
	Amiodarone	Sulfinpyrazone
	Fluconazole	
CYP2D6		
Fluoxetine	Terbinafine	Amiodarone
Paroxetine		Sertraline
Quinidine		

*Strong, moderate, and weak inhibitors are those that, in clinical evaluations, cause a $\geq$ fivefold, a two- to fivefold, and 1.25- to twofold increase in the AUC, or more than an 80%, 50% to 80%, 20% to 50% decrease in clearance, of substrates in which $f_m \approx 1$, respectively.

[†]Mechanism-based inhibitor.

From: FDA Draft Guidance. Drug Interaction Studies—Study Design, Data Analysis, and Implications for Dosing and Labeling. September, 2006.

when $fm \approx 1$, and the drug is active, or when the metabolite formed by a minor pathway is active. In the former case, higher drug exposures result in increased response; in the latter case, lower active metabolite exposures and reduced response are expected. Often there are multiple pathways, of which only one may be inhibited, in which case the effect of inhibition will be less profound. Expanding on this thought, and recognizing that $fm \cdot CL_{int} \cdot Cu_{cell} = fm \cdot CL \cdot C$ and that clearance is additive, it follows from Eq. 17-9 that

$$CL_{inhibited} = CL_{normal} \left[\frac{fm}{1 + \frac{Cu_I}{K_I}} + (1 - fm) \right] \quad 17-10$$

For example, even at the highest dose, enoxacin is only able to reduce the (total) clearance of theophylline by approximately threefold, with a corresponding tripling of theophylline half-life. Theophylline is eliminated by demethylation, ring oxidation, and renal excretion. Evidently, enoxacin inhibits only approximately 67% of the total pathways (i.e., $fm = 0.67$). The antidepressant desipramine, metabolized by the CYP2D6 to form 2-hydroxydesipramine, is another example. Quinidine, a potent inhibitor of CYP2D6 ($Cu_I/K_I \gg 1$) that essentially blocks this enzyme, effectively converts (genetically defined) extensive metabolizers of desipramine, in whom this pathway is a major one ($fm \approx 0.75$), to poor metabolizers, with a pronounced fourfold reduction in clearance ($(1 - fm)CL_{normal}$) and a corresponding fourfold prolongation in half-life. In such cases, the clinical consequences of an interaction depend on the relative contributions of drug and metabolite to efficacy and toxicity. With desipramine, the dose in extensive metabolizers should be reduced to avoid toxicity, if quinidine, or any other strong inhibitor of CYP2D6, is coadministered. As might be expected, quinidine has little effect on the pharmacokinetics of desipramine in the already poor CYP2D6 metabolizer phenotype, because the affected pathway is a minor one in such an individual.

It is important to be able to estimate the potential increase in exposure associated with a drug interaction involving inhibition, especially for drugs with a narrow therapeutic index. This estimate can be obtained for a given dose of drug by appropriately substituting Eq. 17-10 into Eq. 17-4, rearranging, and realizing that $AUC = C_{av,ss} \cdot \tau$, to yield

$$\frac{AUC_{inhibited}}{AUC_{normal}} = \frac{F_{inhibited}}{F_{normal}} \left[\frac{1}{\frac{fm}{1 + \frac{Cu_I}{K_I}} + (1 - fm)} \right] \quad 17-11$$

where $AUC_{inhibited}/AUC_{normal}$ is the ratio of AUCs in the presence and absence of the inhibitor, and $F_{inhibited}/F_{normal}$ is the corresponding ratio of bioavailabilities. Figure 17-8 shows the AUC ratio as a function of Cu_I/K_I and fm assuming bioavailability remains unchanged, which is often, but not always so, as discussed subsequently. The impact of fm is clearly evident. If, for example, a dose adjustment becomes necessary when the AUC ratio increases beyond 50%, it is clear that this condition is met when $Cu_I/K_I = 0.5$ for a drug with $fm = 1$, is 0.8 when $fm = 0.75$, and is never met when $fm \leq 0.5$. Conversely, by rearrangement of Eq. 17-11, one can calculate the modification in dosing rate needed to maintain the AUC within the normal range

$$\frac{(Dose/\tau)_{inhibited}}{(Dose/\tau)_{normal}} = \frac{F_{normal}}{F_{inhibited}} \left[\frac{fm}{1 + \frac{Cu_I}{K_I}} + (1 - fm) \right] \quad 17-12$$

For example, for the condition $fm = 0.75$ and $Cu_I/K_I = 2$, and again assuming bioavailability is unchanged, the dosing rate needed to maintain the normal AUC is 50% of the normal dosing rate. The other consideration is the dosing interval, bearing in mind that the decrease in clearance causes a corresponding prolongation in half-life. The normal practice would be to reduce the dose and maintain the dosing interval, but occasionally,

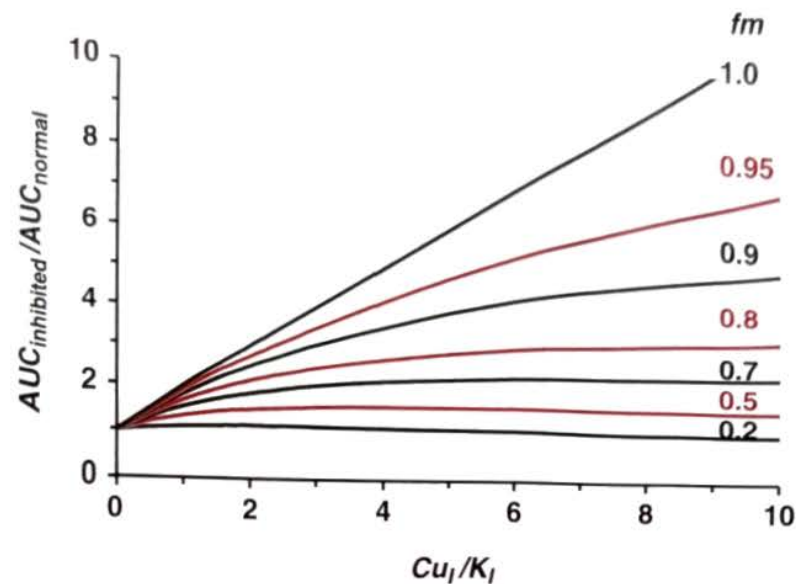


FIGURE 17-8. Prediction of the ratio of the AUC of a drug, following either a single dose or within a dosing interval at steady state, during the presence and absence of a reversible inhibitor as a function of the unbound inhibitor concentration, Cu_i , relative to its K_i , for various values of f_m , the fraction of the drug normally eliminated via the affected pathway. It is assumed that only one pathway of elimination is inhibited, that the inhibitor produces no change in the bioavailability of the drug, and that the unbound concentration of the inhibitor remains constant throughout the elimination of the drug. Notice that, for example, the condition of AUC ratio equals 2 is only met when $f_m > 0.5$, and then at lower Cu_i values the closer f_m is to 1.

it may be more appropriate to make the adjustment by a mixture of some reduction in dose and a lengthening of the dosing interval, particularly for drugs normally given frequently. Examples of drugs that are substrates of either CYP3A4 or CYP2D6, for which oral AUC increases by at least fourfold when a strong inhibitor is coadministered, are listed in Table 17-5.

Much of the foregoing has centered on changes to exposure at steady state. But equally important is the temporal aspect of an interaction that has been mentioned when discussing the enoxacin–theophylline interaction but which can be more profound for drugs with $f_m \approx 1$. In this case, if inhibition causes a 10-fold reduction in clearance of the

TABLE 17-5 Substrates Showing at Least a Fourfold Increase in Oral AUC When Coadministered With a Strong Inhibitor

CYP3A Substrates		CYP2D6 Substrates*
Brecanavir	Perospirone	Atomoxetine
Buspirone	Quetiapine	Desipramine
Darunavir	Saquinavir	Dextromethorphan
Ebastine	Sildenafil	Metoprolol
Everolimus	Simvastatin	Nortriptyline
Felodipine	Tipranavir	Perphenazine
Lovastatin	Triazolam	Tolterodine
Midazolam	Vardenafil	
Nelfinavir	Voriconazole	

*Data in extensive metabolizers.

drug, there is a corresponding 10-fold increase in its half-life. Thus, a drug with normal half-life of 12 hr (0.5 day) becomes one with a 5-day half-life, so that even if this change occurred abruptly, it would take approximately 1 month to achieve the full 10-fold increase in the average concentration of the inhibited drug. In practice, it would take even longer, partly because it takes time for the inhibitor to reach its plateau and hence produce its maximum degree of inhibition on this regimen, and partly because as the inhibitor concentration rises in time to its plateau, so does the degree of inhibition. This, in turn, causes a continuous increase in the half-life of the inhibited drug and it is this continuous change that further prolongs the time to achieve the new plateau of the inhibited drug, as illustrated in Fig. 17-9. One consequence of this potentially insidious but progressive and potentially profound rise in inhibited drug concentration is that an adverse event, associated with the concentration reaching some critical value, may not occur for some time, perhaps several weeks, after the perpetrating drug has been added to the regimen of the patient, and neither patient nor prescriber may associate the cause of the toxicity with the comedication.

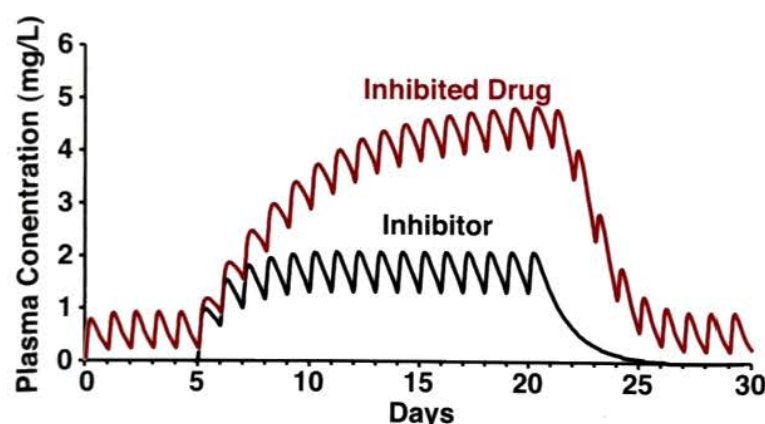


FIGURE 17-9. Inhibition can cause an insidious but profound increase over time in the plasma concentration of a drug when the inhibited pathway is normally the major route of elimination of the inhibited drug. The explanation lies in the progressive decrease in clearance, and hence prolongation in half-life of the inhibited drug, colored line, as the inhibitor, black line, rises toward its plateau. Initially short in the absence of the inhibitor, so that steady state is rapidly reached, the half-life of the inhibited drug can increase from a relatively few hours to several weeks, which in turn results in the rise of the concentration of the inhibited drug taking many weeks before the new, and much higher, plateau is reached. Toxicity associated with these higher concentrations may therefore not become apparent for some time after the inhibitor has been added, and may not be identified as the cause of the toxicity.

A last point here is also noteworthy. Patients may be receiving several moderate or weak competitive inhibitors of an enzyme. When each is administered alone the change in *AUC* of the inhibited drug may be considered too small to warrant a dose adjustment, but when multiple inhibitors are concurrently taken the net inhibition of the enzyme may be sufficiently great to perhaps warrant classifying the combination of inhibitors as a “strong inhibitor,” necessitating a reduction in dose of the inhibited drug or seeking alternatives.

Route of Administration. To address the quantitative questions, and in particular make quantitative predictions, one outstanding question remains: What value should be used for C_{u_i} , the unbound inhibitor concentration? In vitro, the answer is clear; it is the unbound concentration at the enzyme (or transporter) site. However, in vivo this site cannot be sampled directly and a reasonable surrogate is needed. When dealing with events occurring in most organs of the body, the answer is still reasonably clear; it is the unbound systemic inhibitor concentration. This is less appropriate for events occurring

in the liver during absorption of an inhibitor administered orally. Then the portal, and hence the hepatic blood, concentration perfusing the liver may be the appropriate measure because it can be very much higher than that in the systemic circulation, especially for inhibitors that are subject to a high first-pass hepatic extraction and have large volumes of distribution, a point considered in Chapter 7, *Absorption* (Eqs. 7-5 and 7-6) when discussing saturable oral absorption. Accordingly, the degree of inhibition can be much greater when the same dose of inhibitor is given orally than parenterally, with the impact of this difference expected to be greatest during the absorption phase of those drugs that are normally subjected to a high first-pass metabolic loss. Supportive data are provided in Table 17-6, which show that the increase in the *AUC* of orally administered lovastatin, a drug predominantly eliminated by CYP3A metabolism and subject to a high oral first-pass metabolic loss, is greater when the inhibitor diltiazem is given orally than intravenously, despite similar systemic exposures of diltiazem. What clouds an unambiguous assignment of this route effect of diltiazem solely to portal events is the unknown, but likely, significant contribution to increased systemic lovastatin exposure as a result of inhibition of its gut wall CYP3A-catalyzed metabolism by oral diltiazem.

TABLE 17-6 Impact of Route of Administration of Diltiazem on the Extent of Inhibition of Oral Lovastatin

Route of Administration of Diltiazem	Mean Diltiazem Concentration ($\mu\text{g/L}$)	<i>AUC</i> of Lovastatin ($\mu\text{g}\cdot\text{hr/L}$)		Lovastatin <i>AUC</i> Ratio (With Diltiazem/Alone)
		Lovastatin Alone	Lovastatin During Diltiazem Treatment	
Intravenous*	73–140 [†]	64 (37)**	81 (43)	1.27
Oral [†]	130 (58)	60 (25)	214 (109)	3.57

*Single 20-mg oral dose of lovastatin given alone and during an i.v. protocol of diltiazem (20-mg loading dose with constant-rate input 10 mg/hr for 13 hr). (From: Masica AL, Azie NE, Brater DC, et al. Intravenous diltiazem and CYP3A-mediated metabolism. *Br J Clin Pharmacol* 2000;50:273–276.)

[†]Single 20-mg oral dose of lovastatin given alone and after 2 weeks of 120-mg diltiazem orally. (From: Azie NE, Brater DC, Becker PA, et al. The interaction of diltiazem with lovastatin and pravastatin. *Clin Pharmacol Ther* 1998;64:369–77.)

[‡]Range of mean diltiazem plasma concentration in subjects.

**Mean (standard deviation).

Notwithstanding this uncertainty, as a corollary to the route effect of the inhibitor, a route effect for inhibited drug is expected with a greater increase in systemic exposure when it is administered orally than parenterally, again particularly for drugs that are subject to a high first-pass loss. Evidence supporting this last expectation is demonstrated with the fluconazole–midazolam interaction. Displayed in Fig. 17-10 are midazolam data when given intravenously and orally with increasing oral doses of the inhibitor, fluconazole (100–400 mg). These data confirm the graded nature of such interactions, with a greater inhibitory effect seen at the higher doses of fluconazole for both routes of administration of midazolam. They also show an almost twofold greater increase in *AUC* following oral (5.6-fold higher following 400-mg fluconazole than control) than i.v. (twofold higher following 400-mg fluconazole than control) midazolam. Recall from Table 7-3 (page 193) that midazolam is subject about equally to gut wall and hepatic first-pass metabolic loss. Given both i.v. and oral midazolam for each of the doses of fluconazole administered, it is possible to partition the corresponding change in bioavailability, which increased from a control value of 24% to 63% when the 400-mg dose of fluconazole is

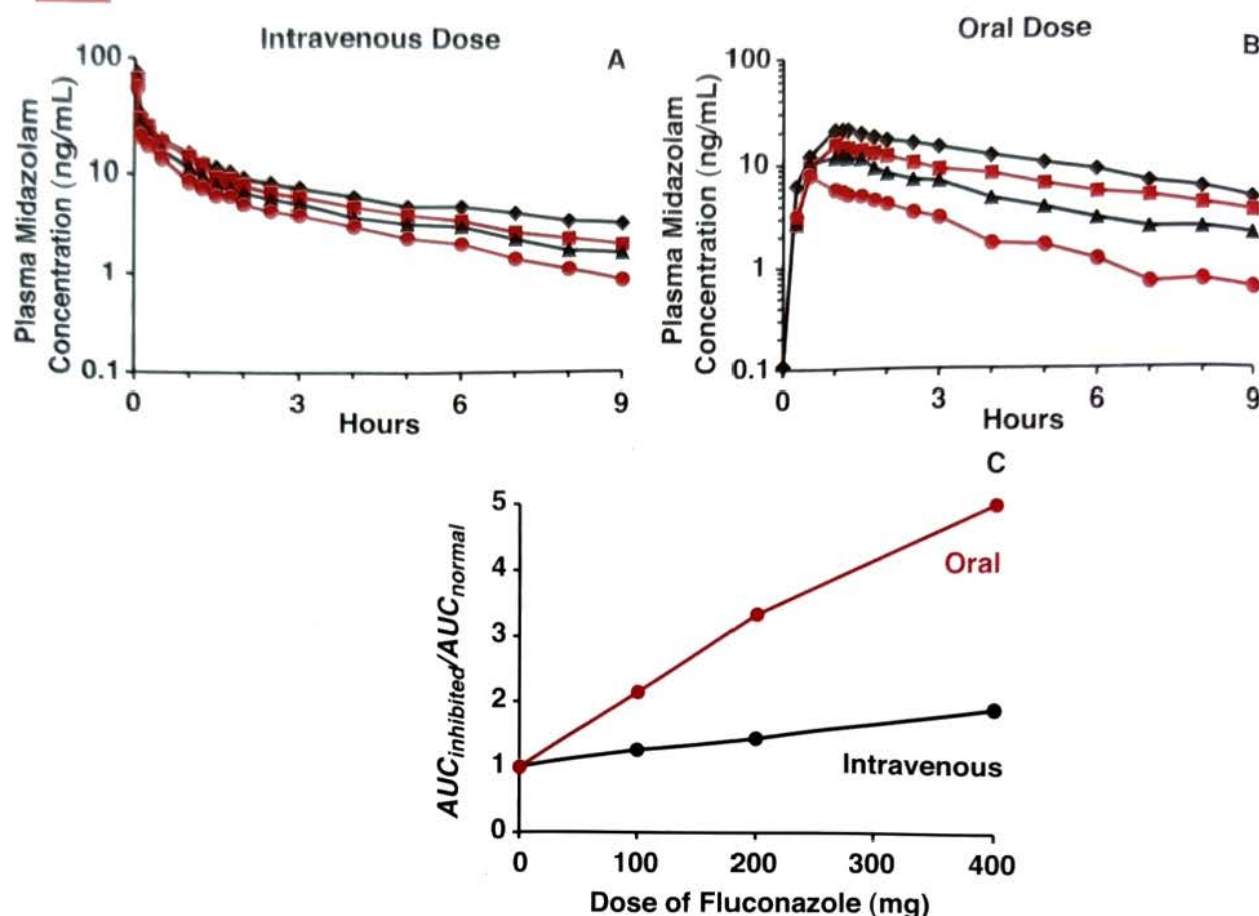


FIGURE 17-10. The inhibition of midazolam, which is almost entirely eliminated by CYP3A catalyzed metabolism, by fluconazole is graded as evidenced by the increase in mean plasma concentrations of midazolam following (A). intravenous (1 mg) and (B). oral (3 mg) administration to a panel of 12 healthy adults, alone (●) and on separate occasions with 100-mg (▲), 200-mg (■), and 400-mg (◆) fluconazole, each given as a single oral dose 2 hr prior to the midazolam administration. C: Plots of $AUC_{inhibited}/AUC_{normal}$ ratio against dose of fluconazole for oral and i.v. midazolam confirm the graded nature of the inhibition and also show that for any dose of fluconazole, the increase in AUC over control is greater following oral than i.v. midazolam administration. (From: Kharasch ED, Walker A, Hoffer C, Sheffels P. Sensitivity of intravenous and oral alfentanil and pupillary miosis as minimally invasive and noninvasive probes for hepatic and first-pass CYP3A activity. *J Clin Pharmacol* 2005;45:1187–1197.)

administered, to events occurring at these two sites, by noting that $F = F_G \cdot F_H$ and that an estimate of $F_H (= 1 - E_H)$ can be made from the corresponding i.v. data. Analysis indicates that F_H increased from 0.42 to 0.72 and F_G from 0.57 to 0.88. Almost complete inhibition of gut wall metabolism is not surprising given that the gut wall is exposed to very high concentrations of oral fluconazole. More generally, the expectation is that the impact of inhibition of gut wall first-pass loss on systemic exposure will be greatest for those drugs that are normally subject to a high extraction there, such as tacrolimus and atorvastatin, and least for those with minimal loss there, such as nifedipine (see Table 7-3 in Chapter 7, *Absorption*).

Drug interactions involving inhibition are not restricted just to those involving metabolism. Rosuvastatin (Crestor) is one of the newer potent statins. It is hydrophilic and largely eliminated unchanged in feces following biliary secretion. It is rapidly taken up by the liver on passage through this organ, where, like all statins, it acts to decrease cholesterol synthesis, and then is secreted into bile with relatively little appearing in the systemic circulation following oral administration, thereby minimizing the risk of systemic toxicity. It works effectively, and in common with other hydrophilic predominantly excreted statins, such as pravastatin, it is minimally subjected to metabolically mediated drug interactions. However,

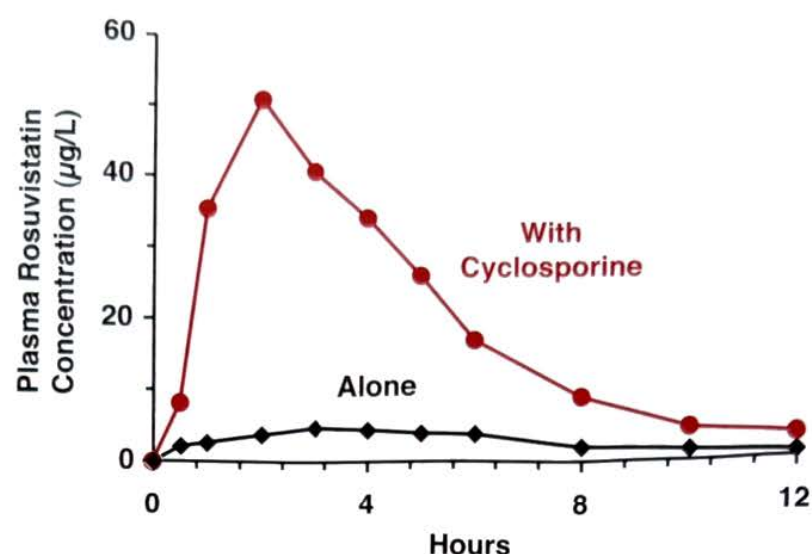


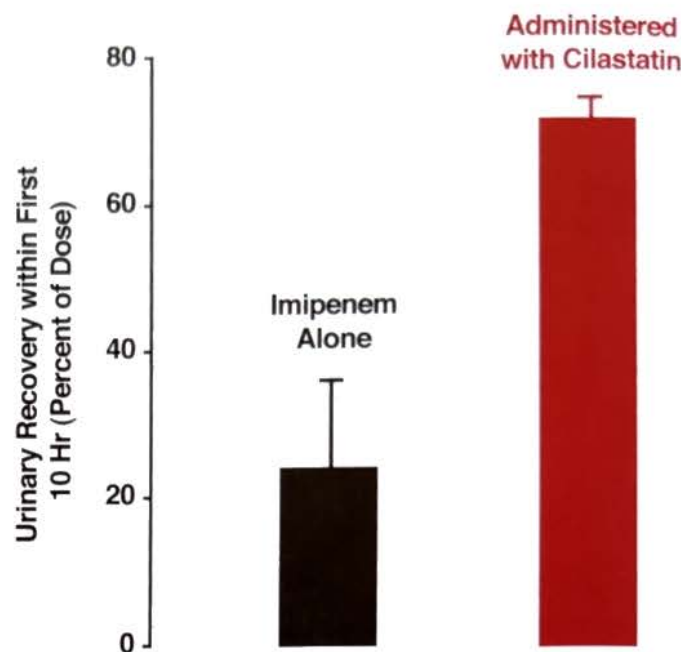
FIGURE 17-11. Cyclosporine inhibits the elimination of rosuvastatin, a drug primarily excreted unchanged in bile and urine. Shown are mean plasma rosuvastatin concentration–time plots within an interdosing interval at steady state in heart transplant recipients, on cyclosporine therapy to reduce the risk of organ rejection, after multiple dosing of 10-mg rosuvastatin once daily (●), and in healthy subjects receiving the same 10-mg multiple-dose regimen of rosuvastatin without cyclosporine (◆). (From: Simonson SG, Raza A, Martin PD, et al. Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. *Clin Pharmacol Ther* 2004;76:167–177.)

as shown in Fig. 17-11, cyclosporine caused, on average, an 11-fold increase in C_{max} and a sevenfold increase in AUC of rosuvastatin administered orally to heart transplantation patients, with even greater increases in some of the patients. The explanation lies primarily in cyclosporine inhibiting the hepatic transporter OATP1B1 (and perhaps other transporters) involved in the uptake of rosuvastatin, so that more escapes hepatic loss and enters into the systemic circulation. Inhibition by cyclosporine of biliary secretion of rosuvastatin and of intestinal efflux transporters that may be involved in absorption may also contribute to the increase in systemic exposure. Clearly, an i.v. arm in the study would have allowed the separation of changes in absorption and clearance processes.

Beneficial Interactions. As mentioned previously, advantage is taken of some drug interactions. A few elaborations are in order here. Penicillin–probenecid combination therapy is an example of the successful use of a drug interaction. Both of these acidic drugs are renally secreted by an anionic transport system. Probenecid competitively inhibits the renal secretion of penicillin, thereby substantially reducing its renal clearance, the major component of total clearance. Consequently, in the presence of probenecid, higher than usual and prolonged plasma concentrations of penicillin are achieved following a normal dosage regimen of the antibiotic. Of note is the lack of a major effect of penicillin on probenecid elimination. Although probenecid is also actively secreted into the kidney tubule, unlike penicillin, it is lipophilic and mostly reabsorbed. Consequently, the renal clearance of probenecid is low; metabolism is its major route of elimination.

Another example of a beneficial interaction is that between cilastatin and the antibiotic imipenem. Imipenem is metabolized extensively in the kidney by a dehydropeptidase, located at the brush border of the proximal tubular cell. Consequently, the urinary excretion of intact imipenem is low and often insufficient to guarantee effective treatment of urinary tract infections. To improve the efficacy of imipenem, it is marketed in combination with cilastatin, a dehydropeptidase inhibitor, which markedly increases the urinary excretion of unchanged imipenem (Fig. 17-12).

FIGURE 17-12. Cilastatin markedly increases the urinary excretion of the antibiotic imipenem by inhibiting the dehydropeptidase in the kidney responsible for its metabolism. The urinary recovery of imipenem is shown after a 500-mg i.v. bolus dose administered alone (*black*) and together with an i.v. bolus of 500-mg cilastatin (*color*). (From: Norby SR, Alestig K, Björnegård B, et al. Urinary recovery of N-formimidoyl thienamycin (MK0187) as affected by coadministration of N-formimidoyl thienamycin dehydropeptidase inhibitors. *Antimicrob Agents Chemother* 1983;23:300–307.)



Mechanism-Based Inhibition. When a normal oral regimen of 500-mg clarithromycin twice daily is administered, the average plateau plasma concentration is approximately 0.7 mg/L. The fraction unbound in plasma is 0.25. In vitro, this macrolide antibiotic inhibits CYP3A4 with a K_I of 7 mg/L. Based on these data, which yields a Cu_I/K_I of 0.025, clarithromycin is not expected to be even a weak inhibitor of CYP3A4. However, as the data in Fig. 17-13 show it is a strong inhibitor that markedly increases the AUC of midazolam, a substrate of CYP3A4, whether midazolam is administered orally (sevenfold increase) or intravenously (2.7-fold increase). How can this be? One possibility is that the portal concentrations of clarithromycin perfusing the liver are much higher than those occurring systemically. But with absorption of this antibiotic relatively slow and clearance low, the additional contribution of absorbed drug to the rising recirculating systemic

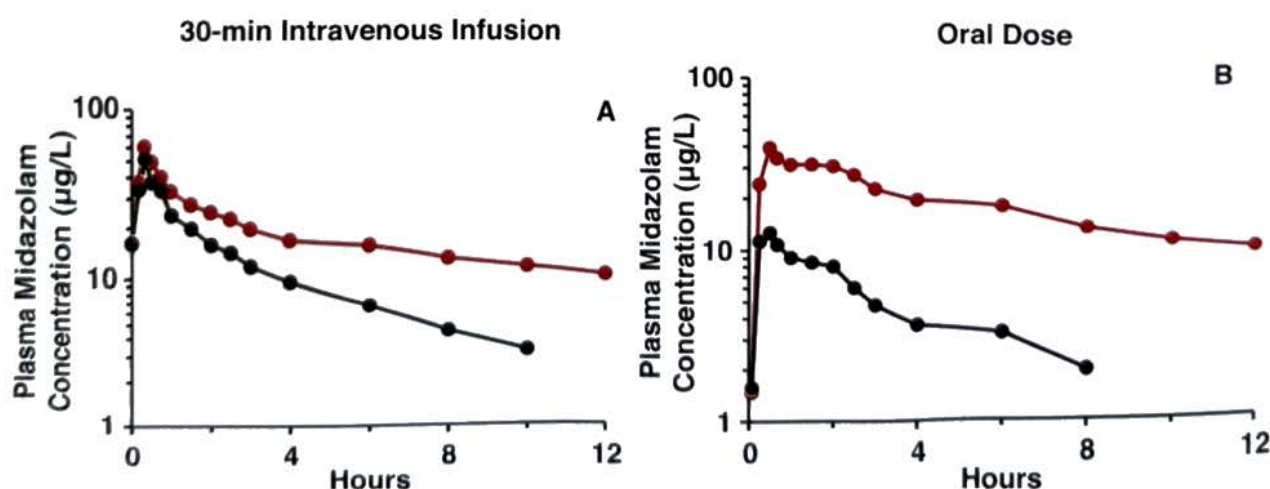


FIGURE 17-13. Clarithromycin irreversibly inactivates CYP3A, the enzyme responsible for the metabolism of midazolam. Shown are semilogarithmic plots of mean plasma concentration versus time of midazolam and $^{15}\text{N}_3$ -midazolam, a stable isotope label, after simultaneous (A) i.v. (0.05-mg/kg midazolam over 30 min) and (B) oral (4-mg $^{15}\text{N}_3$ -midazolam) administration to a group of 16 subjects alone (●) and on day 7 of a daily oral regimen of 500-mg clarithromycin twice daily (●). Clarithromycin causes a decrease in clearance and an increase in oral bioavailability of midazolam. (From: Gorski JC, Jones D, Haehner-Daniels BD, et al. The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. *Clin Pharmacol Ther* 1998;64:133–143.)

clarithromycin in the portal blood is modest, and fails to explain the magnitude of the interaction assuming reversible inhibition. The explanation lies in mechanism-based inhibition, whereby clarithromycin forms a metabolic intermediate complex with the heme moiety of CYP3A4, inactivating this enzyme. With the enzyme effectively consumed, its level in the liver falls, because its synthesis rate, which is unaffected, can no longer keep up with this additional rate of loss above that of the normal rate of degradation of CYP3A4. Accordingly, with less enzyme present, and with V_m directly proportional to the amount of enzyme, it follows that the associated intrinsic clearance of a substrate, in this case clarithromycin, falls. Two important questions remain to be addressed. First, how can a compound with a low Cu_I/K_I be a strong inhibitor? Second, how long does it take to restore the enzyme to the preclarithromycin level on removing this inhibitor?

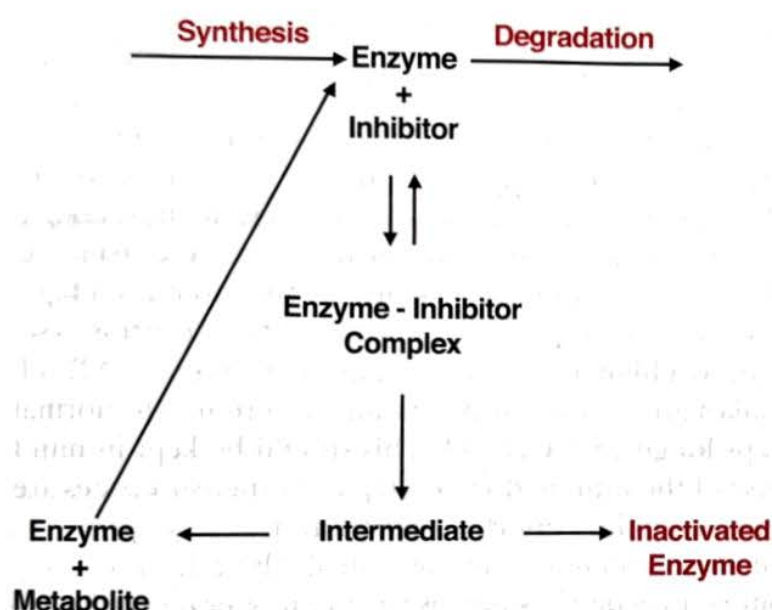


FIGURE 17-14. Scheme depicting mechanism-based inhibition. Drug complexes with enzyme to form a reactive intermediate part of which irreversibly reacts with, and inactivates, the enzyme and part is converted to a metabolite, liberating enzyme to reengage in the process. Normally, enzyme is in steady state with rate of degradation, with associated rate constant, matching the rate of synthesis, but the extra loss by the inhibitor causes a depletion in the level of enzyme.

To address these questions, consider the simple scheme depicted in Fig 17-14. As with conventional kinetics, the inhibitor first rapidly and reversibly binds to the enzyme to form an enzyme-inhibitor complex, which then produces a reactive intermediate, part of which reacts and consumes the enzyme and part forms a stable metabolite, liberating the enzyme to reengage in the process. In addition, the enzyme is turning over; that is, it is being continuously formed and degraded. Analysis of this scheme yields the following relationship for the formation clearance of the substrate in the presence and absence of the inhibitor

$$CL_{f,inhibited} = CL_{f,normal} \left[\frac{1}{1 + k_{inact} \frac{Cu_I}{K_I \cdot k_E}} \right] \quad 17-13$$

or, if fm is the fraction of drug normally eliminated by the affected pathway, then

$$CL_{inhibited} = CL_{normal} \left[\frac{fm}{1 + k_{inact} \frac{Cu_I}{K_I \cdot k_E}} + (1 - fm) \right] \quad 17-14$$

where k_{inact} is the rate constant that relates the maximum rate of inactivation of the enzyme by the inhibitor to the amount of active enzyme remaining, and k_E is the endogenous degradation rate constant, or fractional turnover rate, of the enzyme. It should be noted that inactivation of the enzyme only involves the inhibitor. Accordingly, Eq. 17-13 applies equally to all drugs that are substrates for the enzyme, whereas Eq. 17-14 additionally incorporates the drug-specific parameter, fm .

On comparing Eqs. 17-10 and 17-14, we see that the ratio Cu_I/K_I in Eq. 17-10 is replaced by $k_{inact} \frac{Cu_I}{K_I \cdot k_E}$ in Eq. 17-14. That is, k_{inact}/k_E acts as the modifier on Cu_I/K_I . Estimates for the k_E of CYP3A4 vary, but it is in the order of 0.23 day^{-1} , which corresponds to a half-life of approximately 3 days, although even longer estimates have been reported. Hence, this enzyme turns over, and so is replenished, very slowly. In contrast, inactivation of the enzyme by clarithromycin is relatively fast with k_{inact} gained from in vitro studies of loss of enzyme activity with time on addition of clarithromycin, is 0.07 min^{-1} , so that $k_{inact}/k_E = 438$. That is, for midazolam ($fm \approx 1$), the reduction in clearance caused by the mechanism-based inhibition of CYP3A4 by clarithromycin is expected to be 11-fold ($1 + 438 \times 0.025$) rather than 1.025-fold ($1 + 0.025$) had clarithromycin only been a reversible inhibitor. This anticipated increase is somewhat higher but in the same order as observed in vivo (see Fig. 17-13). Also, because it is the enzyme that is effectively removed, a reduction in clearance, and an associated increase in systemic exposure, would occur with any other CYP3A4 substrate that a patient may be receiving.

Now to the question of time. In contrast to competitive inhibition, removal of the inhibitor, even instantly, does not lead to an immediate restoration of enzyme activity to the preinhibitor level in the case of mechanism-based inhibition. Rather, the time course of return is slow, governed by the normal half-life (or turnover time) of the enzyme. As discussed in Chapter 10, *Constant-Rate Regimens*, when discussing the turnover of endogenous compounds, the situation is analogous to going from a low plateau (in this case, caused by inactivation of the enzyme) to a higher one (once all inhibitor is removed) following a constant-rate infusion; it takes approximately 3.3 half-lives to return to normal activity, at least 2 weeks, and perhaps longer, for CYP3A4. This should be kept in mind when considering adjustment in dose of the inhibited substrate, or if other substrates are added to the regimen of a patient in whom the inhibitor is withdrawn.

Mechanism-based inhibitors are more common than was initially thought (see Table 17-5) and, as with reversible inhibitors, may be classified as strong, moderate, and weak inhibitors, except that, in addition to Cu_I/K_I , this classification also depends on k_E , a measure of the effectiveness of an inhibitor to inactivate the enzyme.

Before leaving this section on inhibition, several additional comments are warranted. First, the maximum exposure in genetically poor metabolizers when one of the other available pathways is inhibited, compared with extensive metabolizers under normal conditions on the same regimen, a measure of potential risk, can be very substantial, as the following calculation shows. Let CL_{EM} , CL_{PM} , be the clearances of a drug in extensive and poor metabolizers in the absence of the inhibitor, and $CL_{PM,inhibited}$ be the clearance in the poor metabolizers in the presence of the inhibitor. Furthermore, assume that the nonpolymorphic pathway subject to inhibition, CL_{NP} , and other unaffected pathways, CL_O , are the same in both groups, then

$$CL_{EM} = CL_{POLY} + CL_{NP} + CL_O \quad 17-15$$

$$CL_{PM} = CL_{NP} + CL_O \quad 17-16$$

and

$$CL_{PM,inhibited} = CL_O = (1 - fm_{POLY} - fm_{NP}) \cdot CL_{EM} \quad 17-17$$

where fm_{POLY} , fm_{NP} are the fractions of total clearance in extensive metabolizers associated with the polymorphic and nonpolymorphic metabolic pathways. It then follows that

$$\frac{\text{Maximum Exposure Ratio}}{AUC_{EM}} = \frac{AUC_{PM,inhibited}}{AUC_{EM}} = \frac{1}{(1 - fm_{POLY} - fm_{NP})} \quad 17-18$$

from which it is seen that, the larger the value of fm_{POLY} , the greater is the AUC expected in poor metabolizers in the presence of the inhibitor compared with that in extensive

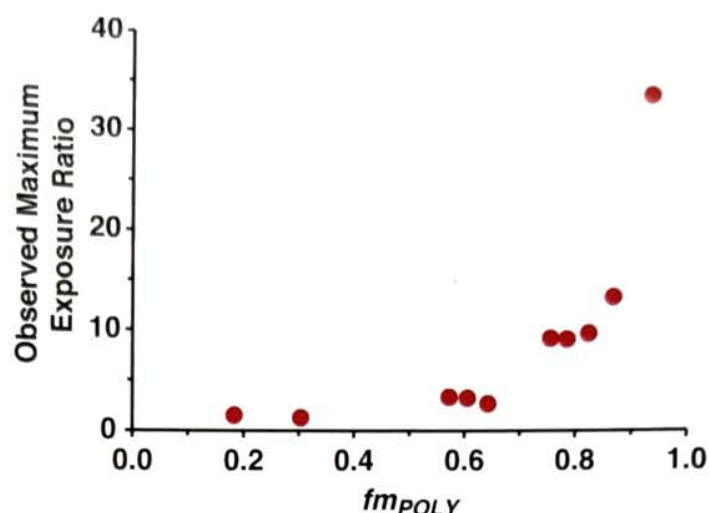


FIGURE 17-15. Plot of observed maximum exposure ratio in poor metabolizers for various drugs when coadministered with an inhibitor of a nonpolymorphic pathway versus the fraction of clearance in extensive metabolizers eliminated by the polymorphic pathway, fm_{POLY} . The substrate–inhibitor pairs on increasing fm_{POLY} values are citalopram–troleandomycin, diazepam–diltiazem, dolasteron–aprepitant, venlafaxine–ketoconazole, pimozide–clarithromycin, R-lansoprazole–clarithromycin, omeprazole–ketoconazole, S-lansoprazole–clarithromycin, omeprazole–troleandomycin, and omeprazole–clarithromycin. (From: Collins C, Levy R, Ragueneau-Majlessi I, Hachad H. Prediction of maximum exposure in poor metabolizers following inhibition of nonpolymorphic pathways. *Curr Drug Metab* 2006;7:295–299.)

metabolizers. Evidence supporting this analysis is shown in Fig. 17-15, in which it is seen that when fm_{POLY} reaches 0.75, exposure ratios in the order of 10 or more occur when one of the other pathways is strongly inhibited, often reason indeed to reduce the dose in poor metabolizers. Notice also that, in addition to fm_{POLY} , the critical factor determining the magnitude of the maximum exposure in poor metabolizers is the presence of other pathways of elimination not affected by the inhibitor.

Second is the general observation that there are far fewer important pharmacokinetically mediated drug interactions occurring extrahepatically. For example, despite the risk of increased brain exposure of many central nervous system (CNS) active P-glycoprotein (PgP) substrates resulting from inhibition of this efflux transporter, there are very few reports of significant CNS interactions, by drugs that in vitro studies clearly demonstrate are inhibitors of this transporter. However, they do exist. One example is the increase in cerebrospinal fluid exposure of ritonavir produced by orally administered ketoconazole, an inhibitor of PgP. Another example is the increased CNS depressive effect of loperamide produced by quinidine, another inhibitor of PgP. A metabolic interaction can be discounted, because loperamide is primarily eliminated by CYP3A oxidation, whereas quinidine at therapeutic doses is an inhibitor of CYP2D6. The reason for this relative paucity of systemically mediated clinically significant interactions is that for most drugs, therapeutic systemic concentrations are well below those needed to cause substantial inhibition of transporters and enzymes. Also, bear in mind that the site of inhibition of PgP is intracellular and with the high inherent barrier property of the cerebral capillaries, the concentration of a drug at the inhibitor site may be lower than exists systemically. For similar reasons, there are few significant drug interactions at the renal level, but again they do exist and are sometimes beneficial, such as the penicillin–probenecid interaction discussed previously, although effective doses of probenecid are at the gram level. Also, for the same reason, there is a tendency for fewer and often less severe drug interactions caused by parenterally than orally administered drugs. Lastly, drug interactions, occurring in the gut wall and liver during the absorption phase of reversible inhibitors, can sometimes be reduced by administering the drug and the inhibitor at different times of the day.

INDUCTION

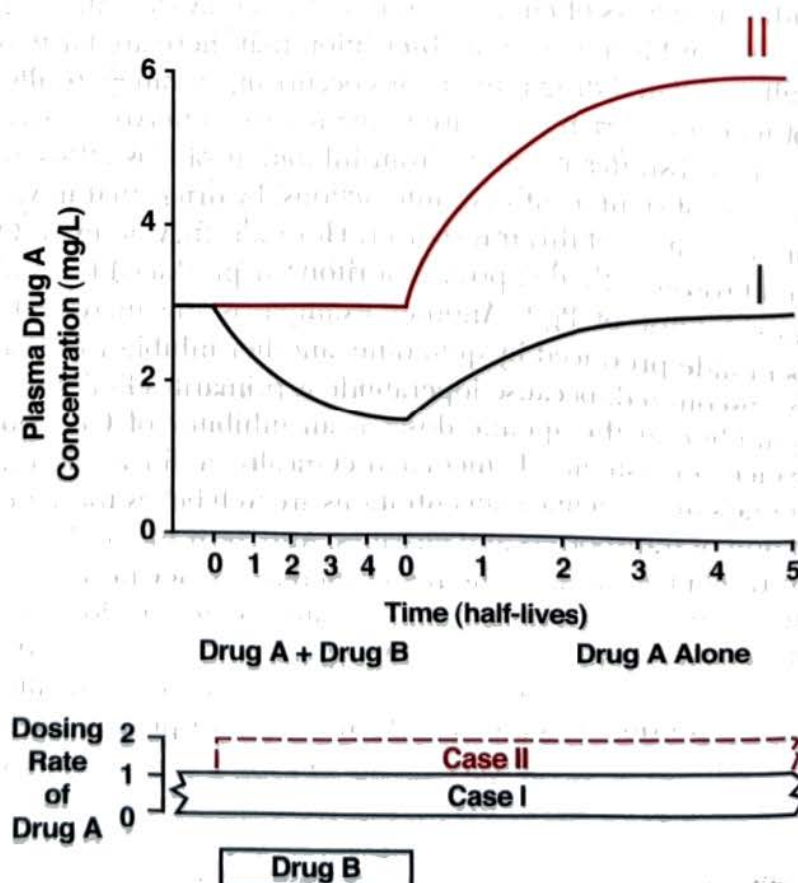
A major cause of increased unbound clearance is induction of an enzyme, or more occasionally a transporter, when it influences elimination. Induction involves an increase in the rate of synthesis of the enzyme or transporter. Kinetic consequences of an increased clearance were discussed in Chapter 5, *Elimination*, and Chapter 7, *Absorption*. The implications of these changes on dosage requirements and the events that follow the addition or withdrawal of drug causing increased clearance are now presented.

In general, as with inhibition, dosage regimen adjustment is required only when the clearance of the affected pathway is or becomes a significant fraction of total drug clearance. Thus, a need to change the dose is anticipated if the clearance associated with a particular pathway, previously 20% of total clearance, were to increase sixfold, because total drug clearance is then doubled. No change in dose is anticipated, even if clearance associated with that pathway increases 20-fold, if this clearance contributes only 1% to total clearance. An exception arises when the metabolite formed is either the active species or is toxic, because its plasma concentration is then greatly increased.

The events depicted in Fig. 17-16 illustrate salient consequences of an increased clearance. In this illustration, a patient stabilized on one drug (Drug A) also receives another (Drug B) that doubles the clearance of Drug A. If the dosing rate of Drug A is not changed, then its concentration falls by one half, at a rate determined by the half-life of the drug *in the presence of Drug B* (Case I). The fall in concentration can be avoided by doubling the rate of administration of Drug A for as long as Drug B is given (Case II). However, a problem of excessive accumulation of Drug A exists if the higher dosing rate is maintained when Drug B is withdrawn. Because the half-life of Drug A is generally longer when given alone, especially for a drug of low extraction ratio, it follows that the time taken to reach a plateau is longer in the absence than presence of Drug B.

Two major assumptions were made in constructing the curves in Fig. 17-16, namely that the effect of Drug B is achieved instantly and remains constant as long as it is administered, and that the effect immediately disappears upon its withdrawal. In practice, both assumptions are invalid.

FIGURE 17-16. When a patient stabilized on Drug A also receives Drug B, a drug that increases the clearance of Drug A twofold, the plasma concentration of Drug A falls (Case I) unless the dosing rate is doubled (Case II, colored). The problem of excessive accumulation arises if administration of Drug A is not reduced to the previous rate when administration of Drug B is stopped. Note that the time to reach plateau is less in the presence, than in the absence, of Drug B and that the time scale in both the presence and absence of Drug B is expressed in half-lives of Drug A.



Enzyme induction was mentioned as the prime cause of increased metabolic clearance. However, a change in clearance is an indirect measure of the effect of an inducer; the direct effect is an increase in the synthesis rate of the drug-metabolizing enzyme. Accordingly, there is a delay between the direct effect and its reflection in the measured response, as amply discussed when considering turnover concepts in Chapter 10, *Constant-Rate Input*. Thus, even if the plasma concentration of the inducer were attained instantly and then maintained, the clearance of the affected drug would increase with time as the enzyme level rises from one plateau value to another. Similarly, there is a delay in the decrease in clearance of the affected drug on removing the inducer. The time delay depends, like other systems in the body, on the kinetics of both the drug and the enzyme involved.

When elimination of enzyme is a slower process than that of the drug, then changes in clearance of the affected drug are determined by the half-life of the enzyme. Clearance may continue to rise even though the concentration of the inducer is maintained relatively constant, until the enzyme has reached a new higher plateau. When, however, elimination of the inducer is the rate-limiting step, changes in the concentration of inducer are then reflected almost instantaneously by changes in the amount of enzyme and hence clearance of the affected drug. This last possibility may explain the effect of phenobarbital on the temporal changes in the plasma concentration of dicumarol and prothrombin time, a measure of its anticoagulant effect, in a patient chronically receiving dicumarol, an oral anticoagulant once prescribed as an alternative to warfarin (Fig. 17-17). Both the fall in the concentration and effect of this drug following phenobarbital treatment have been attributed to the barbiturate, inducing the enzymes responsible for dicumarol metabolism. It takes approximately 3 to 4 weeks for the plasma dicumarol both to fall to a minimum during phenobarbital administration and to return to the prebarbiturate value after phenobarbital is discontinued. Phenobarbital ($t_{1/2}$ of 4 days) also takes approximately the same period of time to reach a plateau in the body and to be eliminated. Thus, the observations are compatible with the hypothesis that the induced enzyme system responds relatively rapidly to changes in plasma phenobarbital concentration.

The data in Fig. 17-17 suggest that prothrombin time may be maintained at the prebarbiturate value by raising the dose of dicumarol during phenobarbital administration. An increased risk arises, however, if the dose of anticoagulant is not reduced when phenobarbital is discontinued. The plasma dicumarol concentration then rises insidiously, as

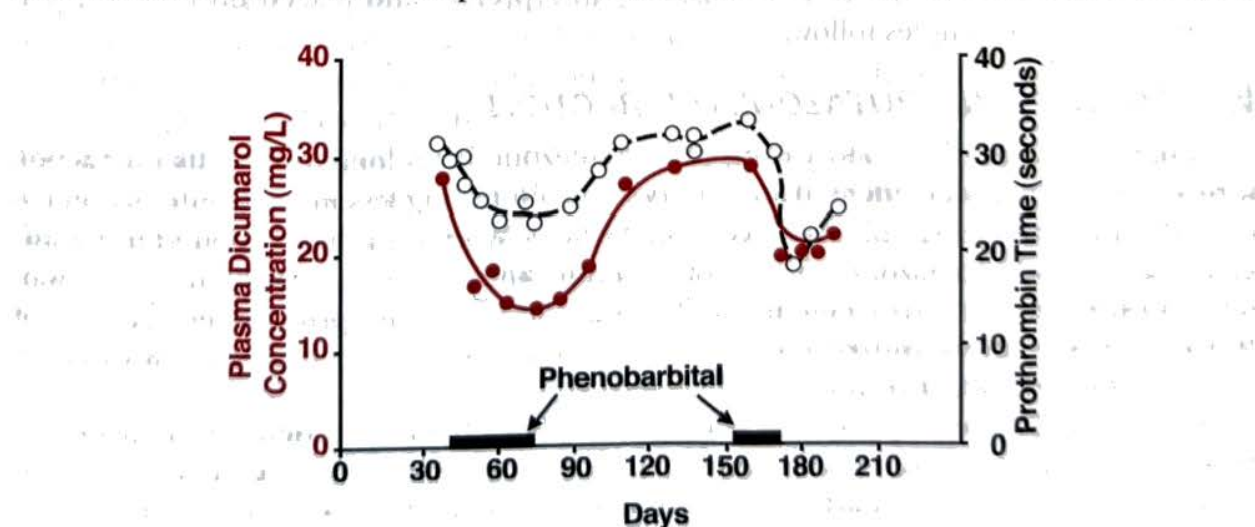


FIGURE 17-17. Administration of phenobarbital (60 mg daily) to a patient receiving dicumarol chronically (75 mg daily) reduces, through induction, the plasma concentration of the anticoagulant (●) and prothrombin time (○), a measure of its effect on the concentration of the vitamin K₁-dependent clotting factors. The time course of the events is largely controlled by the kinetics of phenobarbital, half-life 4 days. (From: Cucinell SA, Conney AH, Sansur MS, Burns JJ. Lowering effect of phenobarbital on plasma levels of dicumarol and diphenylhydantoin. *Clin Pharmacol Ther* 1965;6:420–429.)

phenobarbital is slowly eliminated, and may go unnoticed for several weeks after discontinuing the barbiturate until, perhaps, a hemorrhagic crisis occurs.

Another dimension that influences the time course of changes in enzyme levels is that, as with most processes, induction is a graded effect, such that as the concentration of inducer changes so does the degree of induction, and hence clearance of the affected drug. The net effect is that the time to achieve a new plateau of enzyme content, and hence new clearance of induced drug, following initiation or withdrawal of a constant-rate regimen of inducer, will be longer than that expected had induction instantaneously reached the condition at plateau or ceased.

OTHER CAUSES OF ALTERED CLEARANCE

Unbound clearance can be altered in numerous ways other than inhibition or induction of metabolism and secretion. The lower hepatic clearance of lidocaine when given together with propranolol, a β -adrenergic blocking drug, is an example of a physiologically mediated pharmacokinetic interaction. Propranolol diminishes cardiac output and hence hepatic blood flow, which, in turn, reduces the clearance of lidocaine, a drug highly extracted by the liver. Presumably, because the degree of β -adrenergic blockade is a graded response, the interaction with lidocaine is dependent on the plasma concentration of propranolol.

Raising urine pH by giving acetazolamide or sodium bicarbonate increases the renal clearance of salicylic acid and other acids whose renal clearance is pH sensitive. Giving ammonium chloride or ascorbic acid to make the urine more acidic increases the renal clearance of pH-sensitive basic drugs. Some drugs increase the metabolic clearance of other drugs. They do so most commonly by inducing the drug-metabolizing enzymes, but they may also activate enzymes or retard enzyme degradation. Occasionally, like glucagon, they increase hepatic blood flow and thereby increase the hepatic clearance of drugs that are highly extracted by the liver.

MULTIFACETED INTERACTIONS

So far, emphasis has been on examining drug interactions involving alteration in one process. In practice, several processes may be altered and great care and attention are needed to ensure that the data are correctly interpreted, and placed into clinical perspective. Several examples follow.

WARFARIN-PHENYLBUTAZONE INTERACTION

Although the anti-inflammatory drug phenylbutazone is no longer used, its interaction with warfarin is well documented and offers some interesting lessons. The interaction has caused serious bleeding episodes, occasionally fatal. Warfarin is highly bound in plasma to albumin. Phenylbutazone, devoid of inherent anticoagulant activity, displaces warfarin. Consequently, displacement had been advocated as the primary mechanism for this interaction and sensitized the clinical community to be concerned about displacement interactions, a concern that still lingers.

Figure 17-18 shows the temporal effects of phenylbutazone administration on the plasma and unbound concentrations of warfarin in a subject who ingested 10-mg warfarin daily. The half-life of warfarin is approximately 2 days, and therefore, as anticipated, a steady state is reached within the first 12 days, when warfarin alone is administered. At this time, the warfarin plasma concentration is approximately 4 mg/L and only 0.5% ($C_u = 0.02$ mg/L) is unbound (i.e., $f_u = 0.005$). Warfarin is completely absorbed, and its clearance, estimated by dividing the daily dosing rate by the steady-state plasma concentration, is 0.1 L/hr. Thus, warfarin is a highly bound drug with a low extraction ratio.

Phenylbutazone is also poorly cleared, is highly bound ($f_u = 0.004$ – 0.010), and has a half-life (approximately 3 days), even longer than that of warfarin. Accordingly, when on

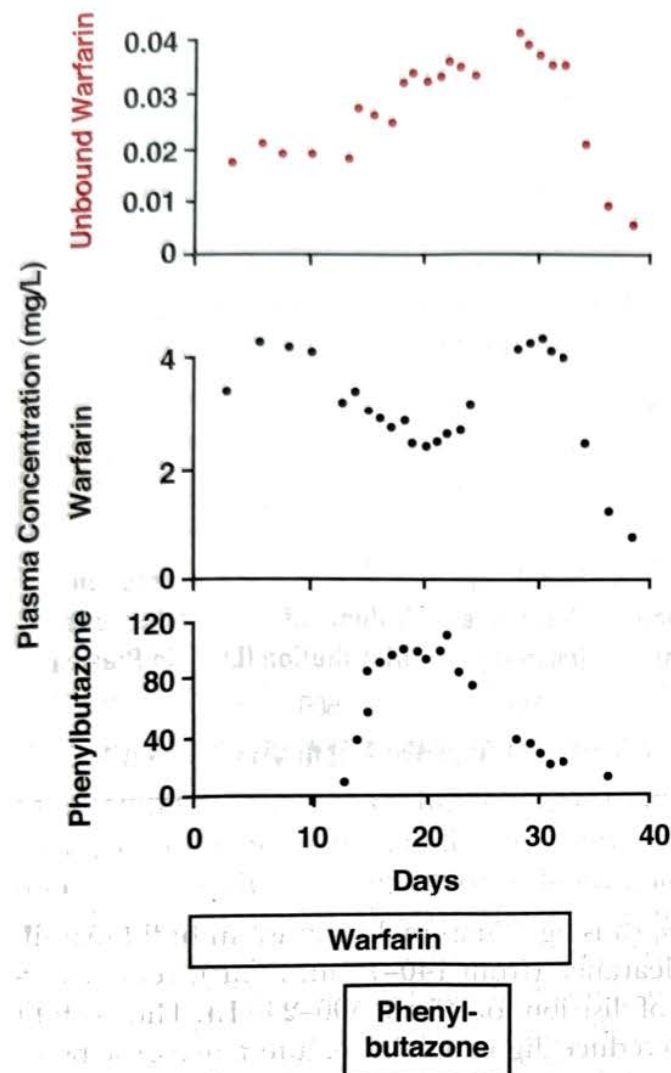


FIGURE 17-18. Warfarin–phenylbutazone interaction. A subject received 10-mg warfarin orally each day and 100-mg phenylbutazone 3 times a day on days 13 to 22. As the phenylbutazone concentration rose, bound warfarin was displaced, and the plasma warfarin concentration fell. The sustained elevation in the unbound warfarin during phenylbutazone administration implies inhibition of warfarin elimination. (From: Schary WL, Lewis RJ, Rowland M. Warfarin–phenylbutazone interaction in man: a long term multiple-dose study. *Res Commun Chem Pathol Pharmacol* 1975;10:633–672.)

day 13, the subject commences the formerly recommended dosage regimen of phenylbutazone, 100 mg 3 times a day, the plasma concentration of this drug rises and eventually reaches a plateau of approximately 100 mg/L, after approximately 10 days. During this period, the plasma warfarin concentration falls steadily in half, to 2 mg/L, and the value of f_u for warfarin rises approximately threefold.

At this point, the events in plasma appear remarkably similar to those depicted in Fig. 17-4 for a pure displacement interaction. However, there is one important difference. The unbound warfarin concentration rises and remains elevated during phenylbutazone administration. Because the effect of warfarin is related to its unbound concentration, this sustained elevation is in accord with the observed sustained augmentation of the effect as long as phenylbutazone is coadministered. Examination of Eq. 17-3 indicates that to account for the elevated values of unbound drug, either the rate of entry of warfarin into the body is increased or the value of CL_{int} is decreased. As the dosage regimen of warfarin is unaltered and warfarin is fully bioavailable, CL_{int} must have decreased.

Warfarin is almost exclusively metabolized in the liver to either weakly active or inactive metabolites. Thus, a lower value for CL_{int} implies a decrease in the ability of the liver to metabolize warfarin. Analysis of several metabolites of warfarin in both plasma and urine subsequently confirmed that, indeed, phenylbutazone inhibits warfarin elimination, and it is this inhibition, and not displacement, that accounts for the clinical picture.

The interaction between phenylbutazone and warfarin is even more complex than portrayed above. Commercial warfarin is a racemate, and the S(–) isomer is five times more active than the R(+) isomer. Phenylbutazone primarily inhibits the formation of 7-(S)-hydroxywarfarin, the major metabolite of the more active isomer. The lesson is clear: Drug interactions can be complex; careful observations are required to unravel the facts.

DIGOXIN-QUINIDINE INTERACTION

Although many patients with cardiovascular diseases have been comedicated with digoxin and the antiarrhythmic agent quinidine over the past 50 years, it is only relatively recently that serious drug interactions have been identified with this combination, probably because such patients tend to experience a relatively high incidence of adverse events from various causes and identifying the specific contribution of each is difficult. The primary cause of the interaction is attributed to an increase in the plasma concentration of digoxin, a narrow therapeutic index drug. Table 17-7 summarizes the pharmacokinetics of digoxin in the absence and presence of quinidine. Quinidine alters all pri-

TABLE 17-7 Typical Pharmacokinetic Parameters of Digoxin in the Absence and Presence of Quinidine

	Oral Bioavailability	Clearance (mL/min)	Renal Clearance (mL/min)	Volume of Distribution (L)	Fraction Unbound in Plasma
Alone	0.75	140	101	500	0.79
With quinidine*	0.85	72	51	240	0.79

*When the $C_{av,ss}$ of quinidine is 1 to 3 mg/L.

mary digoxin pharmacokinetic parameters, causing a marginal increase in oral bioavailability and a twofold decrease in (total) clearance (from 140–72 mL/min), renal clearance (from 101–51 mL/min), and volume of distribution (from 500–240 L). The twofold reduction in clearance dictates the need to reduce digoxin daily maintenance dose by an equal degree. When employed, the loading dose of digoxin also needs to be reduced by half given the twofold reduction in volume of distribution, if excessively high-plasma concentrations of digoxin during digitalization are to be avoided. But what are the mechanisms that explain these changes?

Digoxin is a large molecule (781 g/mol), minimally bound to plasma proteins ($f_u = 0.79$) but extensively distributed to tissues ($V = 500$ L). It is minimally metabolized, with 75% of its clearance associated with renal excretion. Initially, the mechanism associated with the change in each pharmacokinetic parameter was viewed separately. However, much may be explained by a common mechanism: inhibition by quinidine of transporters involved in digoxin pharmacokinetics. Digoxin is a substrate of the efflux transporter Pgp, which is thought to be responsible for its normally incomplete systemic absorption. However, as the oral bioavailability of digoxin is already high, at 75%, there is little room for a large increase.

The renal clearance of digoxin, 101 mL/min, is close to glomerular filtration rate (GFR) (120 mL/min), and given its minimal plasma binding ($f_u = 0.79$) and poor permeability characteristics, it had been long thought that digoxin was much like creatinine: filtered and neither secreted nor reabsorbed. The reduction by half by quinidine of digoxin renal clearance challenged this view. Quinidine has no effect on GFR but rather inhibits the tubular secretion of digoxin by Pgp, which resides in the luminal brush border of the renal tubule. However, as a corollary, with $CL_R < f_u \times GFR$, the only explanation is that digoxin must undergo tubular reabsorption. Substitution of f_u , CL_R , and GFR into Eq. 5-18 of Chapter 5, *Elimination*, indicates that 46% of the filtered load must be reabsorbed. But, because in the absence of quinidine the CL_R of digoxin is close to GFR , it follows that normally its tubular secretion and reabsorption are roughly equal.

Digoxin nonrenal clearance ($CL - CL_R$) is also reduced by quinidine, from 39 (140–101) to 21 (72–51) mL/min. The likely explanation is the same as for renal

clearance; quinidine inhibits the hepatic secretion of digoxin by PgP into bile. We are left to explain the reduction in volume of distribution. With no change in f_u , the cause must be a reduction in tissue distribution. Application of Eq. 4-26 of Chapter 4, *Membranes and Distribution*, ($V = V_P + V_{TW} \cdot f_u/f_{uT}$) would suggest that quinidine either reduces the fraction unbound in tissues, f_{uT} , or restricts the aqueous space in tissue into which digoxin distributes, V_{TW} . Normally, one would be reasonably confident in the former explanation and reject the latter. However, another explanation has some merit. Being large and amphiphilic (having a hydrophobic polycyclic core and hydrophilic sugar chain), digoxin does not readily permeate membranes by passive diffusion. It is a substrate for the uptake transporter OATP1B3 and perhaps other uptake transporters. If uptake transport is a significant mechanism for tissue distribution of digoxin, and quinidine inhibits such processes so as to decrease the value of the uptake permeability-area product (P_{uptake}), the effect would be that with less drug entering cells, the effective tissue-to-plasma concentration ratios (Kp), and hence the volume of distribution, of digoxin would be lower (see Eq. 4-29, Chapter 4, *Membranes and Distribution*. $V = V_P + V_{TW} \cdot \frac{P_{uptake}}{P_{efflux}} \cdot \frac{f_u}{f_{uT}}$). Implicit in this explanation is a lower unbound concentration in the affected tissues for a given amount in the body.

ATORVASTATIN-RIFAMPICIN INTERACTION

Atorvastatin, a potent statin, is extensively metabolized with little eliminated unchanged; some of the metabolites are active. Figure 17-19A shows the plasma concentration-time profiles of atorvastatin following administration of a single oral dose alone and during an i.v. infusion of rifampin, a macrolide antibiotic. A marked 10-fold increase in C_{max} and sevenfold increase in AUC are clearly evident, as is a pronounced shortening of the terminal half-life, from 8 to 3 hr, evident from a semilogarithmic plot of the data (Fig. 17-19B). Separate studies indicate that atorvastatin has a high clearance and a low oral bioavailability (14%) because of extensive first-pass metabolism, primarily by CYP3A. Analysis of the interaction data provide interesting findings. Oral clearance (CL/F) of atorvastatin is reduced ninefold from 6.8 to 0.88 mL/hr/kg, and to account for the shorter half-life in the presence of rifampin, V_{ss}/F is reduced even

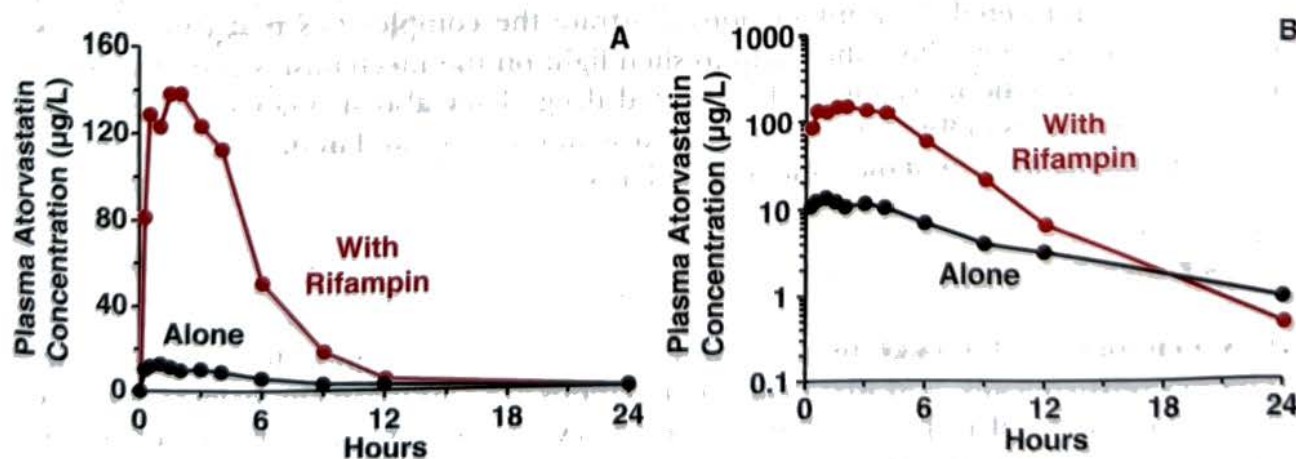


FIGURE 17-19. Rifampin, administered intravenously, increases the systemic exposure of orally administered atorvastatin, and shortens its half-life. **A.** Linear and **(B)** semilogarithmic plots of the mean plasma atorvastatin concentration time profiles in 11 subjects after a single oral dose of 40-mg atorvastatin with (●) and without (●) 600-mg rifampin given as intravenous 30-min infusion. The mechanism involves rifampin inhibiting the hepatic uptake transporter OATP1B1 and perhaps other uptake transport processes in this organ and other tissues. (From: Lau YY, Huang Y, Frassetto L, Benet LZ. Effect of OATP1B transporter inhibition on the pharmacokinetics of atorvastatin in healthy volunteers. *Clin Pharmacol Ther* 2007;81:194–204.)

more, by 17-fold, from 66 L/kg to 3.8 L/kg. Furthermore, most of the area (and hence elimination) of systemically available atorvastatin occurs beyond t_{max} . The most plausible explanation of the AUC data is that rifampin decreases the clearance of atorvastatin and hence first-pass loss, with an associated increase in oral bioavailability. The temptation is to assign the mechanism as one of rifampin inhibiting the metabolism of atorvastatin. Certainly, rifampin is an inhibitor of CYP3A, but studies have shown that inhibition occurs only at much higher concentrations than obtained with rifampin in the current study. The mechanism lies elsewhere.

Atorvastatin is taken up into the liver by the uptake transporter OATP1B1, which rifampin inhibits. In doing so, rifampin moves the rate-limiting step for hepatic elimination of atorvastatin from metabolism to uptake. Clearance is reduced, now becoming sensitive to uptake, and oral bioavailability is increased. Reflect, clearance of an extensively metabolized drug is reduced as a result of inhibition of uptake transport into the eliminating organ; metabolism and transport are clearly intimately coupled. The reason behind the reduction in volume of distribution of atorvastatin by rifampin can be thought of as similar to that by which quinidine may reduce the volume of distribution of digoxin. Atorvastatin acts in the liver, which is a major organ of distribution for this drug. The reduction in its volume of distribution by rifampin is at least in part caused by inhibition of hepatic uptake. Also, inhibition of the distribution of this statin into other tissues cannot be discounted. Note that this strong interaction occurred following intravenously administered rifampin, emphasizing again that a systemically mediated interaction, although relatively uncommon, can and does occur. The magnitude of the interaction depends on the concentrations achieved, and hence on the dosage regimen and pharmacokinetics of the causative drug. In this case, the usual daily dose of rifampin, 600 mg, was administered on a single occasion. Lastly, there are many examples showing that rifampin is an inducer of drug metabolism, especially CYP3A4 (see also Fig. 17-5). Rifampin is a classic strong inducer. However, as also pointed out previously in this chapter, the full effect of enzyme induction takes time to develop, and only becomes apparent during multiple daily dosing of rifampin. Then, it is observed that both atorvastatin C_{max} and AUC fall to even lower values than seen when atorvastatin is administered alone, clearly more than offsetting the inhibitory effect of this macrolide antibiotic, at least at the metabolic and perhaps also at the transporter, level.

These multifaceted drug interactions illustrate the complexities that can, and do, occur, but at the same time, they help to shed light on the mechanisms responsible for the pharmacokinetic behavior of the affected drug. They also strongly emphasize the need to be cautious in the interpretation of drug interactions and in the extrapolation of such data to the clinical management of patients.

PHARMACODYNAMIC INTERACTIONS

It is mentioned at the beginning of this chapter how two or more drugs can interact pharmacodynamically, and that drug combinations are employed clinically to produce a greater beneficial response than can be achieved with any one component or less harm for a given desired response. Such drug combinations are often said to be clinically synergistic. The situation now considered, however, is one involving competition of two drugs for the same receptor, either both acting as agonists or antagonists, although administration of an agonist to offset an antagonist arises in drug therapy, and vice versa. For example, vitamin K is administered to restore the prothrombin time to within the normal therapeutic range in patients inadvertently over anticoagulated with warfarin. Recall from Chapter 3, *Kinetics Following an Intravenous Bolus Dose*, that the intensity of a graded response, E , can be related to concentration through the

relationship

$$E = \frac{E_{max} \cdot C^\gamma}{C_{50}^\gamma + C^\gamma} \quad 17-19$$

which, on dividing top and bottom by C_{50}^γ , the potency of the drug and rearrangement gives

$$\frac{E}{E_{max}} = \frac{\frac{C^\gamma}{C_{50}^\gamma}}{1 + \frac{C^\gamma}{C_{50}^\gamma}} \quad 17-20$$

Now consider two full agonists, A and B, competing for the same target. Each can elicit the same maximum response, E_{max} , when administered alone. Assuming that the steepness factor, γ , is the same, then the fraction of the maximum response produced in the presence of the two drugs is

$$\frac{E}{E_{max}} = \frac{\frac{Cu_A^\gamma}{Cu_{50,A}^\gamma} + \frac{Cu_B^\gamma}{Cu_{50,B}^\gamma}}{1 + \frac{Cu_A^\gamma}{Cu_{50,A}^\gamma} + \frac{Cu_B^\gamma}{Cu_{50,B}^\gamma}} \quad 17-21$$

where subscripts A and B denote the two drugs. The important feature of this relationship is that the presence of one drug effectively increases the C_{50} value of the other. Accordingly, as shown in Fig. 17-20, however, much of the concentration of Drug B is increased in the presence of Drug A; E_{max} cannot be exceeded. The closer the response achieved with drug alone is to E_{max} , the lower the impact on addition of the other.

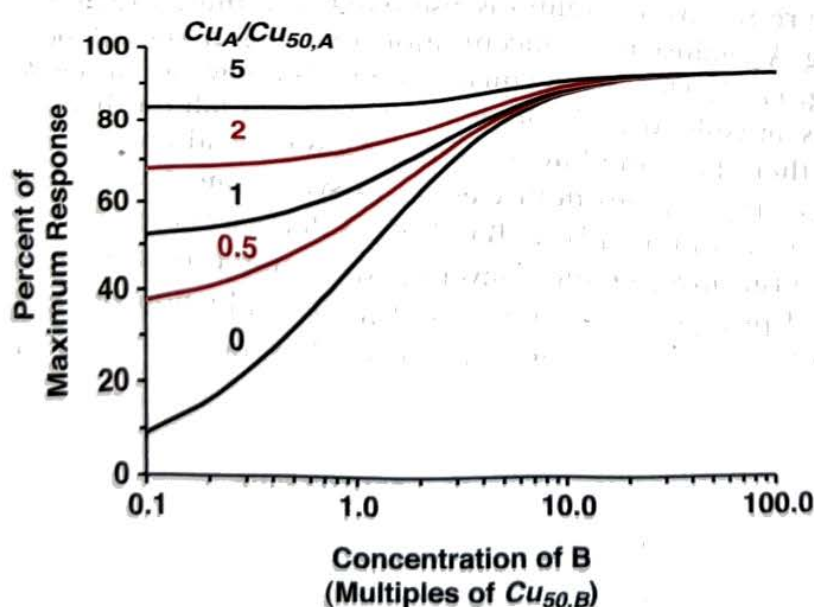


FIGURE 17-20. When two drugs, Drug A and Drug B, are full agonists (or antagonists) the effect of Drug B on Drug A depends on the percent of the maximum response achieved by Drug A in the absence of Drug B. The closer to E_{max} achieved with Drug A alone, the smaller the impact of adding Drug B.

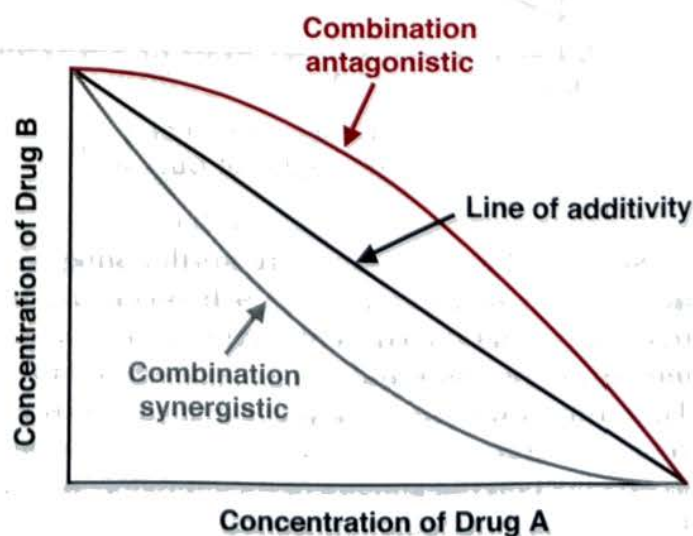
Several additional points are worth noting. First, in principle, there is no distinction in the form of the relationship between the degree of inhibition of an enzyme or transporter and the concentrations of two competitive inhibitors, and that between the intensity of response and the concentrations of two agonists competing at a receptor site. The primary difference in practice is that with many pharmacokinetic interactions, the concentration of inhibited drug is often well below its K_m (or K_T), so that it has minimal to no effect on the kinetics of the inhibitor, (i.e., the drug interaction is unidirectional). In contrast, with pharmacodynamic interactions, because most drugs only produce a

measurable therapeutic effect above baseline when the concentration is at or above its C_{50} , each drug in the combination will affect the contribution to the total effect of the other. Second, drugs are invariably competing with one or more endogenous compounds for a target, so that in principle one could characterize the relationship between response and drug concentration if one also knew the pharmacodynamic parameters and concentration of the endogenous compound(s). Sometimes, however, the endogenous compound has not been identified, or even if it has been identified and its pharmacodynamic parameters determined, rarely is its concentration at the target site known. Part of the variability in response to a drug between and within individuals is likely to be a result of variability in the concentration of competing endogenous compound. Lastly, situations arise in which one or more of the metabolites of a drug are agonists or antagonists for the same target as the parent compound, an aspect considered in the next chapter, *Metabolite Kinetics and Response*.

One implicit property of Eq. 17-21 is that the drug combination is **additive**. But what does additivity mean in the context of pharmacodynamics when inherently, response is nonlinearly related to concentration? To address this question, imagine the simple case of two full agonists, that for each $\gamma = 1$, and that when given alone, Drug A produces 50% E_{max} that is when $Cu_A = Cu_{50,A}$. Then, to increase the response to 75% E_{max} substitution into Eq. 17-16 shows that Cu_A must be increased to five times $Cu_{50,A}$. Alternatively, 75% E_{max} can be achieved by fixing Cu_A at $Cu_{50,A}$ and adding Drug B at a concentration of $2Cu_{50,B}$. This is readily confirmed by appropriate substitution into Eq. 17-21. That is, Drugs A and B are equivalent when expressed as multiples of their respective potencies (Cu_{50}). The combination is additive in that the response is predictable knowing the potencies of each drug alone or, stated differently, the combination does not lead to any change in the potency of either drug.

One test for additivity is to fix response and vary the concentrations of the two drugs. It follows that if the combination is additive, then the sum of the equivalent concentrations (Cu divided by the respective C_{50} value) is also fixed, and therefore, a plot of the concentration of Drug A against the concentration of Drug B should be a straight line, as depicted in Fig. 17-21. The line of equal response is known as an *isobole*, and the graph is referred to as an **isobologram**. Observations may not fall on this line of additivity but instead fall either above the line, implying a less-than-additive effect, **antagonism**, or below the line, a greater-than-additive effect, or **synergism**. Antagonism can be thought of as one in which addition of Drug B to Drug A decreases the effective potency of Drug A, and synergism involves the converse. An example of synergism is that between midazolam and propofol in hypnosis used in the induction of anesthesia, and an example of antagonism is the decrease in cardiostimulant effect of

FIGURE 17-21. An isobologram comprises a plot of the combinations of the concentrations of two drugs, Drug A and Drug B, that produce a fixed response. When the line of equal responses, the isobole, is straight, the combination is additive. The combination is less-than-additive when the isobole curves above the line of additivity, and synergistic when it curves below the line of additivity.



isoproterenol by β -blockers, such as propranolol. Although an isobologram is a useful means of detecting synergism or antagonism, it does not allow for an accurate assessment of the magnitude of the effect or the mechanism involved. For example, a drug combination may be synergistic either because one of the drugs modifies the receptor, thereby enhancing its interaction with the other drug, or because one drug inhibits the efflux of the other from the cell containing the receptor, thereby raising its internal concentration. Again, definitions are one thing, mechanisms involved and implications to drug therapy may well be another.

We have now explored various sources and causes of variability in drug response. We turn in the next chapter to the integration of this information and the underlying concepts to the initiation and maintenance of drug therapy.

KEY RELATIONSHIPS

$$t_{1/2, \text{inhibited}} = t_{1/2, \text{normal}} \cdot \frac{CL_{\text{normal}}}{CL_{\text{inhibited}}}$$

$$\frac{CL_{\text{inhibited}}}{CL_{\text{normal}}} = \frac{C_{ss, av, \text{normal}}}{C_{ss, av, \text{inhibited}}}$$

$$\text{Rate of metabolism} = \frac{CL_{\text{int}, f} \cdot Cu_{\text{cell}}}{1 + Cu_I/K_I} = \frac{fm \cdot CL_{\text{int}, f} \cdot Cu_{\text{cell}}}{1 + Cu_I/K_I}$$

$$CL_{\text{inhibited}} = CL_{\text{normal}} \left[\frac{fm}{1 + \frac{Cu_I}{K_I}} + (1 - fm) \right]$$

$$\frac{AUC_{\text{inhibited}}}{AUC_{\text{normal}}} = \frac{F_{\text{inhibited}}}{F_{\text{normal}}} \left[\frac{1}{\frac{fm}{1 + \frac{Cu_I}{K_I}} + (1 - fm)} \right]$$

$$\frac{(Dose/\tau)_{\text{inhibited}}}{(Dose/\tau)_{\text{normal}}} = \frac{F_{\text{normal}}}{F_{\text{inhibited}}} \left(\frac{fm}{1 + \frac{Cu_I}{K_I}} + (1 - fm) \right)$$

$$CL_{\text{inhibited}} = CL_{\text{normal}} \left[\frac{fm}{1 + k_{\text{inact}} \frac{Cu_I}{K_I \cdot k_E}} + (1 - fm) \right]$$

$$\frac{\text{Maximum Exposure Ratio}}{AUC_{EM}} = \frac{AUC_{PM, \text{inhibited}}}{AUC_{EM}} = \frac{1}{(1 - fm_{\text{POLY}} - fm_{\text{NP}})}$$

$$\frac{E}{E_{\text{max}}} = \frac{\frac{Cu_A^\gamma}{Cu_{50, A}^\gamma} + \frac{Cu_B^\gamma}{Cu_{50, B}^\gamma}}{1 + \frac{Cu_A^\gamma}{Cu_{50, A}^\gamma} + \frac{Cu_B^\gamma}{Cu_{50, B}^\gamma}}$$

STUDY PROBLEMS

(Answers to Study Problems are in Appendix J.)

- Briefly comment on the accuracy of the following statements.
 - Drug interactions are often detected when an interacting drug is initiated or withdrawn.
 - Displacement of one drug by another occurs when the molar concentration of the “displacer” approaches that of the protein that binds the other drug.
 - Displacement interactions are generally not *therapeutic drug interactions*.
 - Of the various mechanisms of drug interaction, inhibition of metabolism is of primary therapeutic importance.
 - Drug interactions are graded.
 - Drug interactions at the transporter level are likely with class 1 compounds of the Biopharmaceutics Classification System.
- The graphs below show the concentration–time curves following the method of administration given. Sketch the expected plasma concentration–time profile of each drug (low clearance, large volume of distribution) if administered again during the coadministration of another drug that is at steady state. The parameter given is altered twofold. Each graph should clearly indicate the consequence of a change in CL , V , and $t_{1/2}$ (or a combination).

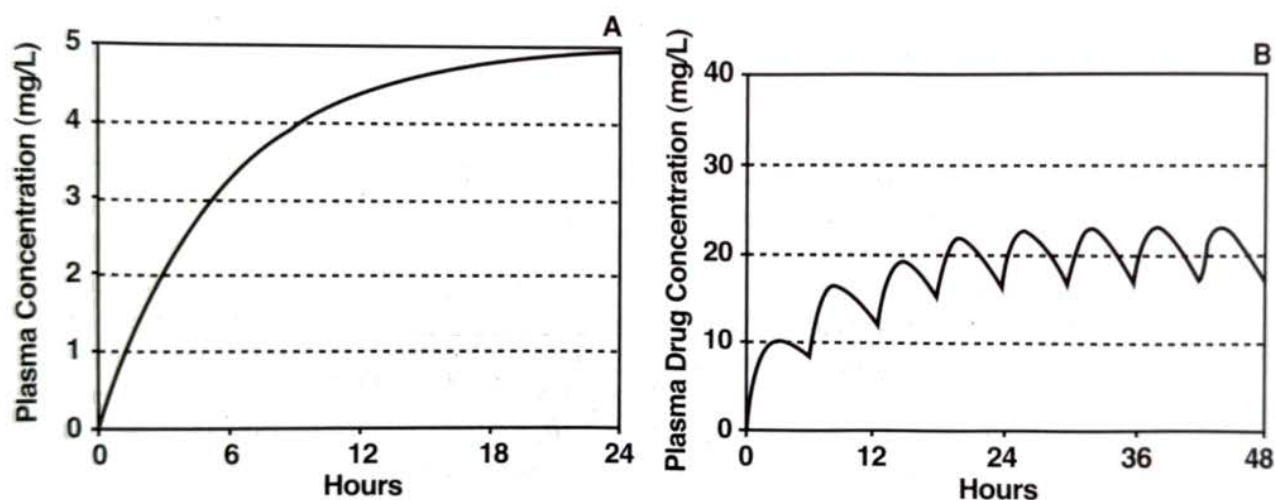


FIGURE 17-22. A. Constant-rate infusion (f_u increased). B. Multiple oral doses (CL_{int} decreased).

- Chlordiazepoxide, a benzodiazepine, was administered to six healthy volunteers (45 mg, i.v. bolus) in crossover fashion alone or in the fifth day of a daily 400-mg dose of ketoconazole, an antifungal agent. For the purpose of this problem, the drug has one-compartment model characteristics. Mean values of $C(0)$ and $t_{1/2}$ for chlordiazepoxide are shown in Table 17-8.

TABLE 17-8 Pharmacokinetics of Chlordiazepoxide Alone and When Given With Ketoconazole

	Without Ketoconazole	With Ketoconazole
$C(0)$ (mg/L)	2.0	2.0
$t_{1/2}$ (hr)	23.9	43.4

From: Brown MW, Maldonado AL, Meredeth CG, et al. Effect of ketoconazole on hepatic oxidative drug metabolism. Clin Pharmacol Ther 1985;37:290–297.

- a. (1) Prepare a semilogarithmic graph of the mean concentration–time profiles of chlordiazepoxide in the presence and absence of ketoconazole. Label both axes and identify both curves.
- (2) Complete the following table:

	Without Ketoconazole	With Ketoconazole
$V(L)$		
$CL (L/hr)$		

- b. Given that chlordiazepoxide is eliminated by biotransformation in the liver, what physiologic mechanism(s) (Q_H , f_u , f_{uT} , CL_{int}) is responsible for the interaction of ketoconazole with chlordiazepoxide? Justify any assumptions that you make.
4. Drug A is given by infusion at a rate of 25 mg/hr to maintain a constant plasma concentration. The data in Table 17-9 are obtained in a subject who is infused at this rate in the absence and presence of Drug B (assume that it is at steady state when present).

TABLE 17-9 Pharmacokinetic Data of a Drug Given Alone and in Presence of Another Drug

Plateau Plasma Concentration of Drug B (mg/L)	Data for Drug A			
	Plateau Plasma Concentration (mg/L)	Urinary Excretion Rate at Steady State (mg/hr)	Fraction Unbound in Plasma	Half-life (hr)
0	10.0	15	0.1	12
20.0	6.7	4	0.3	8

Given this information and the observation that the creatinine clearance in this subject is 100 mL/min,

- a. Determine if there is evidence for Drug A being secreted and/or reabsorbed in the kidneys.
 - b. Is the volume of distribution of Drug A affected by Drug B?
 - c. Determine the mechanism(s) by which Drug B interacts with Drug A.
 - d. Discuss the therapeutic implications of coadministering Drug A and Drug B.
5. Bergstrom et al. studied the pharmacokinetic interaction of the antidepressants fluoxetine and desipramine. Figure 17-23 and Table 17-10 summarize the observations following a single oral dose of desipramine (50 mg) alone and 3 hr after the eighth daily dose of fluoxetine (60 mg each). The concentration of fluoxetine during the time desipramine is quantified remains relatively constant (half-life of fluoxetine = 3–4 days after multiple doses). The value of f_e for desipramine is about 0.03.
- a. Given that the plasma-to-blood concentration ratio of desipramine is close to 1.0, that the drug is metabolized only in the liver, and that the “well-stirred” model of hepatic elimination applies, calculate the value of $f_u \cdot CL_{int}$ in the presence and absence of fluoxetine.

- Suggest one mechanism (combination of mechanisms is not acceptable) for the pharmacokinetic interaction observed. Document how you arrived at your conclusion.
- Briefly explain why the factor by which half-life is altered is not the same as that of CL/F .
- In the current study, a single dose of desipramine was administered on day 8 of daily administration of fluoxetine (half-life = 1.5 days). If administration of desipramine on day 8 had, instead, been the first dose of a once-daily multiple-dose regimen, would you expect the time for desipramine to achieve a steady state to be any different than had the subjects been first administered chronically desipramine to steady state and daily fluoxetine dosing then commenced, while maintaining the regimen of desipramine?
- What implications do the observations of these authors have for the concurrent administration of these two antidepressants? Briefly discuss.

FIGURE 17-23. Mean plasma concentration of desipramine after a 50-mg oral dose given alone (●) and after 8 daily doses (60 mg each) of fluoxetine (●). (From: Bergstrom RF, Peyton AL, Lemberger L. Quantification and mechanism of the fluoxetine and tricyclic antidepressant interaction. Clin Pharmacol Ther 1992;51:239-248.)

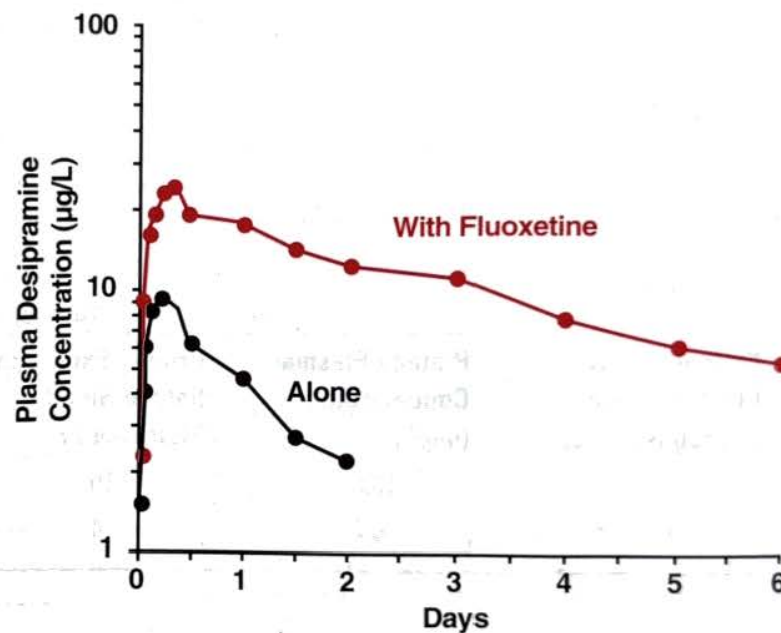


TABLE 17-10 Pharmacokinetic Parameters and Measures (Mean, Standard Deviation) of Desipramine when Administered Orally as a Single 50-mg Dose Alone and after Eight Daily Doses of Fluoxetine

Parameter/Measure	Given Alone (n = 6)	After Multiple Doses of 60 mg/day of Fluoxetine (n = 5)
$AUC(0-\infty)$ ($\mu\text{g} \cdot \text{hr/L}$)	284 ± 244	2110 ± 900
C_{max} ($\mu\text{g/L}$)	9.4 ± 5.4	23.9 ± 5.6
t_{max} (hr)	5.3 ± 1.6	6.8 ± 1.1
$t_{1/2}$ (hr)	16.1 ± 5.2	63.8 ± 19.3
CL/F (L/hr)	289 ± 168	27.1 ± 10.3
V/F (L/kg)	77.1 ± 39.8	29.7 ± 7.7

- Addition of the protease inhibitor ritonavir to the regimen of a patient on digoxin has produced severe digoxin toxicity. Ding et al. studied this interaction by administering a 0.5-mg i.v. bolus of digoxin to subjects alone and on day 3 of an 11-day oral

regimen of a 300-mg ritonavir twice daily, a therapeutic regimen. Table 17-11 summarizes their mean observations. The half-life of ritonavir, a known inhibitor of CYP3A4 and P-gP, is 3 to 5 hr. The majority of digoxin, a substrate of P-gP, is eliminated by a combination of renal and biliary excretion; its oral bioavailability is approximately 80%.

TABLE 17-11 Pharmacokinetics of Digoxin Alone and During Ritonavir Administration

Treatment	Clearance (mL/min)	Renal Clearance (mL/min)	Volume of Distribution (L)	Fraction Excreted Unchanged
Control	409	194	255	0.55
Ritonavir	238	126	451	0.59

From: Ding R, Tayrouz Y, Riedel K, et al. Substantial pharmacokinetic interaction between digoxin and ritonavir in healthy volunteers. Clin Pharmacol Ther 2004;76:73–84.

- Why was digoxin given on day 3 of an 11-day regimen of ritonavir?
 - What is the likely mechanism by which ritonavir reduces the renal clearance of digoxin? Although not measured in the study, the value of f_u of digoxin is close to 0.8, and independent of drug concentration.
 - Does ritonavir affect the nonrenal clearance of digoxin and if so, what is the likely mechanism?
 - Could the mechanism for reduction in renal clearance also be responsible for the increase in volume of distribution?
 - Why is the fraction of digoxin renally excreted not materially changed when coadministered with ritonavir?
 - What is your recommendation concerning the dosage regimen of digoxin if it is to be added onto the regimen of a patient stabilized on ritonavir?
 - On comparing the impact of ritonavir with that of quinidine, discussed in this chapter, what conclusions can be drawn on the likely role of transporters on the tissue distribution of digoxin?
- Normal values for the pharmacokinetic parameters: clearance, fraction unbound in plasma, and fraction excreted unchanged are listed in Table 17-12 for Drugs A through G. Situations are presented that alter the kinetics of each of these drugs. On the right, indicate whether the value of each parameter would be observed to increase ($\uparrow$), decrease ($\downarrow$), or show little or no change ($\leftrightarrow$). Each drug is administered orally and has a volume of distribution greater than 50 L.
 - Tolbutamide, an oral hypoglycemic agent, has the following pharmacokinetic parameters in a 70-kg adult: $F = 1.0$, $V = 9$ L, $CL = 1.1$ L/hr, $f_e = 0.03$. Elimination is almost exclusively via oxidation to hydroxytolbutamide.
 - Calculate the average plateau concentration and time to reach it when tolbutamide is administered in a regimen of 0.5 g orally twice daily.
 - Several drugs inhibit the metabolism of tolbutamide and cause excessive accumulation and hypoglycemic crises, unless the maintenance dose of tolbutamide is reduced. Given the following information about a competitive inhibitor: $F = 1.0$, $V = 13$ L, $CL = 0.6$ L/hr, $f_u = 0.04$, $K_i = 0.6$ mg/L, calculate the following:
 - The expected new average plateau plasma concentration of tolbutamide after the addition of a dosage regimen of 250 mg twice daily of the inhibitor to a patient previously stabilized on tolbutamide. The regimen of tolbutamide is continued unchanged.
 - The time taken to reach this new plateau.

TABLE 17-12 Changes in Pharmacokinetic Parameters of Drugs A to G in Various Situations

Drug	Normal Values			Situations	Observations				
	Clearance* mL/min	Fraction* Unbound	Fraction Excreted Unchanged		Clearance*	Volume of Distribution†	Half-life	Fraction Excreted Unchanged	Oral Bioavailability
A	420	0.5	0.7	Simultaneous administration of a competitive inhibitor of renal secretion					
B (acid, CL_R pH sensitive)	200	0.1	1.0	Urine pH increased by another drug					
C	1200	0.5	0.99	Simultaneous administration of a competitive inhibitor of metabolism of Drug C					
D	1200	0.05	0.01	Simultaneous administration of a drug that displaces Drug D from plasma binding sites					
E	50	0.4	0.5	Simultaneous administration of a drug that displaces Drug E from tissue binding sites					
F	10	0.1	0.01	Simultaneous administration of a drug that displaces Drug F from plasma binding sites					
G	1300	0.7	0.95	Simultaneous administration for several days of an inducer of the enzymes that metabolizes Drug G					

*Based on measurement of drug concentration in blood.

†All drugs have $V_d > 50$ L.

- (3) A practical regimen of tolbutamide that maintains a similar average preinhibitor plateau concentration, when coadministered in the presence of the inhibitor. Tolbutamide is available as a scored 500-mg tablet.
9. A drug has the following pharmacokinetic characteristics: $CL = 870 \text{ mL/min}$, $t_{1/2} = 16 \text{ hr}$, $f_e = 0.01$, $F_{oral} = 0.15$. The low oral bioavailability is caused entirely by first-pass hepatic loss. The metabolites formed are inactive. The drug is likely to be given to patients receiving known enzyme inducers, and you have evidence to suspect that inducible enzymes are responsible for the metabolism of the drug under development. To provide some definitive data, you are asked to design a drug-interaction study in healthy volunteers. As a previous study showed that the kinetics of the test drug upon multiple dosing can be predicted from single dose administration, you decide on a single-dose study in the absence and presence of the potential inducer.
- Would you randomize the study with respect to the treatment sequence?
 - Would you recommend giving the usual recommended dosage regimen of potential inducer?
 - How long would you recommend administering the potential inducer before and after test drug administration?
 - To ensure an adequate determination of the effects of induction, should they occur, would you recommend any change in the usual blood sampling times used to assess the pharmacokinetics of the test drug and if so, at what times and why. To assist, in answering this question, draw on the semilogarithmic plot in Fig. 17-24 the anticipated plasma concentration–time profile to show trends after induction following oral administration of 100 mg of the drug.

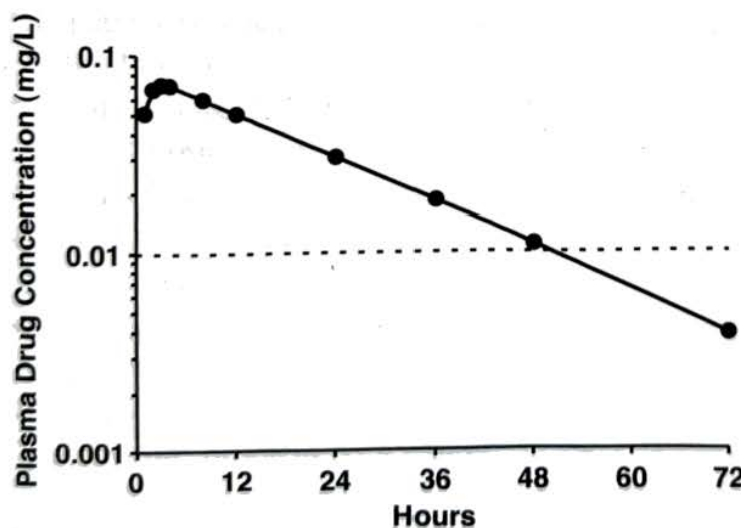


FIGURE 17-24.

- Which of the pharmacokinetic parameter(s) (F , V , CL , $t_{1/2}$, k) best reflects enzyme induction?
10. Diltiazem is thought to be a mechanism-based inhibitor of CYP3A4. It is extensively metabolized, partly via CYP3A4, to some active metabolites, and has a half-life in the range of 4 hr. What is your expectation of the pharmacokinetics of this drug with respect to dose and time dependency, and its effect on the pharmacokinetics of other drugs that are extensively metabolized by CYP3A4? Briefly discuss.